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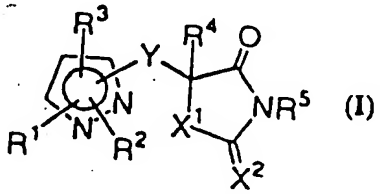
(57) Abstract

A pyrazole type thiazolidine compound of formula (I) and its salt, wherein X^1 is S or O; X^2 is S, O or NH; Y is CR^6R^7 (R^6 is a hydrogen atom, a C_1-C_7 alkyl group or a C_3-C_7 cycloalkyl group, and R^7 is a hydrogen atom, a C_1-C_7 alkyl group or a C_3-C_7 cycloalkyl group, or forms a bond together with R^4); R^1 is a C_1-C_{10} alkyl group, a C_1-C_{10} alkoxy group, etc., or $-V_k$-W_l-Z (Z is a C_3-C_{10} cycloalkyl group, a C_6-C_{14} aromatic group, a C_4-C_{12} heterocyclic aromatic group, etc., V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, and each of k and *l* is 0 or 1), -V-W-V-W-Z, -W-V-W-Z, -V-W-V-Z, or -W-V-Z (V, W and Z are as defined above, and two V's and W's may, respectively, be the same or different); each of R^2 and R^3 is independently a hydrogen atom, a C_1-C_7 alkyl group, etc.; R^4 is a hydrogen atom or a C_1-C_7 alkyl group, etc.; and R^5 is a hydrogen atom or a carboxymethyl group. The compound of formula (I) and its salt are useful for a preventive or curative agent for diabetes mellites and diabetic complications.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DESCRIPTION

TITLE OF THE INVENTION

PYRAZOLYLMETHYL-THIAZOLIDINES USEFUL AS HYPOGLYCEMIC AGENTS

TECHNICAL FIELD

The present invention relates to novel pyrazole type thiazolidines having a hypoglycemic effect and an anti-glycation effect, which are useful in medical and veterinary fields, particularly useful for preventing or treating diabetes mellitus and diabetic complications.

BACKGROUND ART

Heretofore, various sulfonylurea derivatives and biguanide derivatives have been widely used as oral hypoglycemic agents for lowering blood sugar values. However, these agents had disadvantages of causing serious hypoglycemic coma and lactic acidosis revelation, and therefore every possible care must have been taken for practical use. "Chem. Pharm. Bull., vol. 30, p. 3563 (1982)", "J. Med. Chem., vol. 32, p. 421 (1989)", "J. Med. Chem., vol. 34, p. 318 (1991)", "J. Med. Chem., vol. 33, p. 1418 (1990)", Japanese Unexamined Patent Publication No. 64586/1980, and European Laid Open Patent Publications No. 177353, No. 283035; No. 283036, No. 332331, and No. 332332 disclose various thiazolidindiones which achieve a hypoglycemic effect, and these are particularly useful for treating Type II diabetes and are noted as agents for hardly causing such hypoglycemic

symptoms as caused by the above-mentioned oral hypoglycemic agents. However, although these compounds have a function of effectively lowering a blood sugar value, it is not proved that these compounds have effects for reducing or preventing various chronic symptoms caused by diabetes, such as diabetic nephropathy, diabetic cataract, diabetic retinopathy, diabetic neuropathy and the like.

Further, some compounds having a pyrazole methylene bonded to the 5-position of a thiazolidindione ring, have been known. For example, U.S. Patent 3,615,608 discloses N-ethylthiazolidindione derivatives, and Japanese Unexamined Patent Publications No. 204640/1991 and No. 224749/1989 disclose N-sulfoethyl or N-carboxyethyl-thiazolidindione derivatives, as compounds useful for silver halide photographic materials. However, it has never been known that these compounds have a hypoglycemic effect.

On the other hand, non-enzymatic glycosylation of vital protein has been recently noted for causing various diseases accompanied by diabetes and arteriosclerosis. Generally, the reaction of reducing sugars with amino acids and proteins caused by heat treatment of foods or during storing foods is known as Maillard reaction. It was recognized in 1970's that the Maillard reaction is actually caused in a living body, and this reaction is recently called as glycation (see "J. Biol. Chem., vol.

252, p. 2998 (1977)"). Also, it has been proved that glycation is exacerbated in such chronic hyperglycemic state as in diabetes, and it is presumed that the glycation becomes a trigger for causing various diabetic complications (see "New Eng. J. Med., vol. 314, p. 403(1986)"). The process of glycation is not completely clear, but it is considered that various vital proteins are reacted with reducing sugars to non-enzymatically form Schiff base, and that this is crosslinked after causing Amadori rearrangement and is converted to fluorescent browning materials, i.e. AGE (advanced glycosylation end products). It was recognized in rat's diabetic cataract that glycation of crystalline of lens protein is exacerbated. Also, it is presumed that glycation of myelin protein causes diabetic neuropathy and that glycation of collagen and elastin present in connective tissue causes renal dysfunction-inducing thickening of renal glomerular basement membrane and atherosclerosis. Brownlee et al reported that the anti-glycation effect of aminoguanidine prevents formation of AGE protein on arterial walls of a rat suffering from diabetes, and the aminoguanidine becomes remarkable as an agent for preventing diseases including diabetes mellitus (see "Science, vol. 232, p. 1629 (1986)"). However, the above-mentioned function of aminoguanidine is not always sufficient, and an agent achieving an anti-glycation effect satisfactory for practical use has not been found

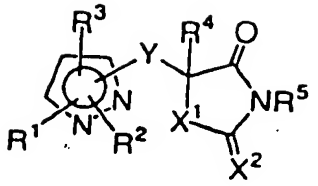
yet.

On the other hand, aldose reductase (AR) is known to be an enzyme for reducing aldoses such as glucose and galactose to polyols such as sorbitol and galactitol in a living body. It is also known that accumulation of the polyols thus produced by the enzyme in organs induces or exacerbates various diabetic complications such as diabetic retinopathy, diabetic neuropathy and diabetic nephropathy, and therefore an inhibitor against this enzyme is useful as an agent for treating these diabetic complications.

Under these circumstances, the present inventors have synthesized various thiazolidines which are not disclosed in the above-mentioned literatures, and have studied their properties. As this result, the present inventors have found a compound having an anti-glycation effect and aldose-reductase inhibitory activities which were not exhibited by the above-mentioned known compounds. Thus, the present invention provides pyrazole type thiazolidines capable of preventing or treating diabetes mellitus and diabetic complications.

DISCLOSURE OF THE INVENTION

The novel pyrazole type thiazolidine derivatives of the present invention are pyrazole type thiazolidines of the following formula (I) and their salts:



(I)

wherein X^1 is S or O;

X^2 is S, O or NH;

Y is CR^6R^7 (R^6 is a hydrogen atom, a C_1-C_7 alkyl group or a C_3-C_7 cycloalkyl group, and R^7 is a hydrogen atom, a C_1-C_7 alkyl group or a C_3-C_7 cycloalkyl group, or forms a bond together with R^4);

R^1 is a C_1-C_{10} alkyl group, a C_2-C_{10} alkenyl group, a C_2-C_{10} alkynyl group, a C_1-C_{10} alkoxy group, a C_2-C_{10} alkenyloxy group, a C_1-C_{10} alkylthio group, a C_1-C_{10} monoalkylamino group or a di-C_1-C_{10} alkylamino group (each of said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyloxy, C_1-C_{10} alkylthio, C_1-C_{10} monoalkylamino and di-C_1-C_{10} alkylamino groups may be substituted with a hydroxyl group or a C_1-C_7 alkyl group), or

$-V_k-W_l-Z$ (Z is a C_3-C_{10} cycloalkyl group, a C_3-C_7 cycloalkenyl group, a C_6-C_{14} aromatic group, a C_4-C_{12} heterocyclic aromatic group (said heterocyclic aromatic group may contain at most 5 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom as constituents for the heterocyclic ring), or a C_4-C_6 heterocycloaliphatic group (said heterocycloaliphatic group may contain at most 3 hetero

atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom as constituents for the heterocyclic ring) (each of said C_3-C_{10} cycloalkyl, C_3-C_7 cycloalkenyl, C_6-C_{14} aromatic, C_4-C_{12} heterocyclic aromatic and C_4-C_6 heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting of a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group),

W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, and

each of k and ℓ is 0 or 1),

-V-W-V-W-Z (V, W and Z are as defined above, and two V's and W's may, respectively, be the same or different),

-W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different),

-V-W-V-Z (V, W and Z are as defined above, and two V's may be the same or different), or

-W-V-Z (V, W and Z are as defined above);

each of R^2 and R^3 is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group (said C_1-C_7 alkyl and C_3-C_7 cycloalkyl groups may be substituted with a hydroxyl group), a phenyl group, a naphthyl group, a benzyl group, a pyridyl group, a pyrimidinyl group, a pyridazinyl group, a furanyl group, a thienyl group, a pyrrolyl group, a pyrazolyl group, an imidazolyl group, a pyranyl group, a quinolyl group, a benzoxazolyl group, a benzothiazolyl group or a benzimidazolyl group (each of said phenyl, naphthyl, benzyl, pyridyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyranyl, quinolyl, benzoxazolyl, benzothiazolyl and benzimidazolyl groups may be substituted with at most 5 members selected from the

group consisting of a hydroxyl group, a C_1-C_7 alkyl group, a C_1-C_7 alkoxy group and a halogen atom), and R^2 or R^3 may further be a halogen atom when it is bonded to a carbon atom at the 3-, 4- or 5-position of the pyrazole ring;

R^4 is a hydrogen atom or a C_1-C_7 alkyl group, or forms a bond together with R^7; and

R^5 is a hydrogen atom or a carboxymethyl group.

The substituents of the compound of the formula (I) of the present invention will be explained with reference to typical examples, but it should be understood that the scope of the present invention is by no means limited by these examples.

Each substituent in the formula (I) will be specifically described hereinafter.

In the definition of R^1:

The C_1-C_{10} alkyl group includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, 1-pentyl, 2-pentyl, 3-pentyl, i-pentyl, neopentyl, t-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-methyl-1-ethyl-n-pentyl, 1,1,2-trimethyl-n-propyl, 1,2,2-trimethyl-n-propyl, 3,3-dimethyl-n-butyl, 1-heptyl, 2-heptyl, 1-ethyl-1,2-dimethyl-n-propyl, 1-ethyl-2,2-dimethyl-n-propyl, 1-octyl, 3-octyl, 4-methyl-3-n-heptyl, 6-methyl-2-n-heptyl, 2-propyl-1-n-heptyl, 2,4,4-trimethyl-1-n-pentyl, 1-nonyl, 2-nonyl, 2,6-dimethyl-4-n-heptyl, 3-ethyl-2,2-dimethyl-3-n-pentyl, 3,5,5-trimethyl-

1-n-hexyl, 1-decyl, 2-decyl, 4-decyl, 3,7-dimethyl-1-n-octyl, and 3,7-dimethyl-3-n-octyl. Preferred is a C_4-C_{10} alkyl group which includes, for example, n-butyl, i-butyl, s-butyl, t-butyl, 1-pentyl, 2-pentyl, 3-pentyl, i-pentyl, neo-pentyl, t-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-methyl-1-ethyl-n-pentyl, 1,1,2-trimethyl-n-propyl, 1,2,2-trimethyl-n-propyl, 3,3-dimethyl-n-butyl, 1-heptyl, 2-heptyl, 1-ethyl-1,2-dimethyl-n-propyl, 1-ethyl-2,2-dimethyl-n-propyl, 1-octyl, 3-octyl, 4-methyl-3-n-heptyl, 6-methyl-2-n-heptyl, 2-propyl-1-n-heptyl, 2,4,4-trimethyl-1-n-pentyl, 1-nonyl, 2-nonyl, 2,6-dimethyl-4-n-heptyl, 3-ethyl-2,2-dimethyl-3-n-pentyl, 3,5,5-trimethyl-1-n-hexyl, 1-decyl, 2-decyl, 4-decyl, 3,7-dimethyl-1-n-octyl and 3,7-dimethyl-3-n-octyl. Each group may be substituted by a hydroxyl group or a C_1-C_7 alkyl group.

The C_2-C_{10} alkenyl group includes, for example, ethenyl, 1-propenyl, 2-propenyl, 1-methylvinyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 1-ethyl-2-vinyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-1-butenyl, 1-i-propylvinyl, 2,4-pentadienyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2,4-hexadienyl, 1-methyl-1-pentenyl, 1-heptenyl, 1-octenyl, 1-nonenyl and 1-decenyl. Preferred is a C_5-C_{10} alkenyl group which includes, for

example, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-1-butenyl, 1-i-propylvinyl, 2,4-pentadienyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2,4-hexadienyl, 1-methyl-1-pentenyl, 1-heptenyl, 1-octenyl, 1-nonenyl and 1-decenyl. Each group may be substituted by a hydroxyl group or a C_1-C_7 alkyl group.

The C_2-C_{10} alkynyl group includes, for example, ethynyl,1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl, 1-nonynyl, and 1-decynyl. Preferred is a C_5-C_{10} alkynyl group which includes, for example, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl, 1-nonynyl and 1-decynyl. Each group may be substituted by a hydroxyl group or a C_1-C_7 alkyl group.

The C_1-C_{10} alkoxy group includes, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy and decyloxy. Preferred is a C_4-C_{10} alkoxy group which includes, for example, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy and decyloxy. Each group may be substituted by a hydroxyl group or a

C_1-C_7 alkyl group.

The C_2-C_{10} alkenyloxy group includes, for example, ethenyloxy, 1-propenyloxy, 2-propenyloxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy, 1-pentenyloxy, 2-pentenyloxy, 3-pentenyloxy, 4-pentenyloxy, 2,4-pentadienyloxy, 1-hexenyloxy, 2-hexenyloxy, 3-hexenyloxy, 4-hexenyloxy, 5-hexenyloxy, 2,4-hexadienyloxy, 1-heptenyloxy, 1-octenyloxy, 1-nonenyloxy and 1-decenyloxy. Preferred is a C_5-C_{10} alkenyloxy which includes, for example, 1-pentenyloxy, 2-pentenyloxy, 3-pentenyloxy, 4-pentenyloxy, 2,4-pentadienyloxy, 1-hexenyloxy, 2-hexenyloxy, 3-hexenyloxy, 4-hexenyloxy, 5-hexenyloxy, 2,4-hexadienyloxy, 1-heptenyloxy, 1-octenyloxy, 1-nonenyloxy and 1-decenyloxy. Each group may be substituted by a hydroxyl group or a C_1-C_7 alkyl group.

The C_1-C_{10} alkylthio group includes, for example, methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, s-butylthio, t-butylthio, pentylthio, hexylthio, heptylthio, octylthio, nonylthio and decylthio. Preferred is a C_5-C_{10} alkylthio which includes, for example, pentylthio, hexylthio, heptylthio, octylthio, nonylthio and decylthio. Each group may be substituted by a hydroxyl group or a C_1-C_7 alkyl group.

The C_1-C_{10} monoalkylamino group includes, for example, methylamino, ethylamino, n-propylamino, i-propylamino, n-butylamino, i-butylamino, s-butylamino, t-butylamino, pentylamino, hexylamino, heptylamino,

octylamino, nonylamino and decylamino. Preferred is a C_5-C_{10} monoalkylamino group which includes, for example, pentylamino, hexylamino, heptylamino, octylamino, nonylamino and decylamino. Each group may be substituted by a hydroxyl group or a C_1-C_7 alkyl group.

The di-C_1-C_{10} alkylamino group includes, for example, dimethylamino, diethylamino, di-n-propylamino, di-i-propylamino, d-n-hexylamino, N-methyl-N-n-pentylamino, N-methyl-N-n-hexylamino, N-methyl-N-n-heptylamino, N-methyl-N-n-octylamino, N-methyl-N-n-nonylamino, and N-methyl-N-n-decylamino. Preferred are, for example, N-methyl-N-n-pentylamino, N-methyl-N-n-hexylamino, N-methyl-N-n-heptylamino, N-methyl-N-n-octylamino, N-methyl-N-n-nonylamino, and N-methyl-N-n-decylamino. Each group may be substituted by a hydroxyl group or a C_1-C_7 alkyl group.

In the definition of Z:

The C_3-C_{10} cycloalkyl group includes, for example, cyclopropyl, 1-methyl-cyclopropyl, 2-methyl-cyclopropyl, 4-methyl-cyclohexyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, 1-adamantyl, and 2-adamantyl. Preferred is a C_6-C_{10} cycloalkyl group which includes, for example, cyclohexyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, 1-adamantyl and 2-adamantyl. Each group may have at most 5

substituents (the substituents may, for example, be a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

The C_3-C_7 cycloalkenyl group includes, for example, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, cyclopentadienyl, 2-bicyclo[2.2.1]heptenyl, and 2,5-bicyclo[2.2.1]heptadienyl. Each group may have at most 5 substituents (said substituents may, for example, be a

hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

The C_6-C_{14} aromatic group includes, for example, phenyl, naphthyl (said naphthyl includes α-naphthyl, and β-naphthyl), indenyl (said indenyl includes 1-indenyl, 2-indenyl, 3-indenyl, 4-indenyl, 5-indenyl, 6-indenyl, and 7-indenyl), indanyl (said indanyl includes 1-indanyl, 2-indanyl, 4-indanyl, and 5-indanyl), and fluorenyl (said

fluorenyl includes 1-fluorenyl, 2-fluorenyl, 3-fluorenyl, 4-fluorenyl, and 9-fluorenyl). Preferred is a C_6-C_{14} aromatic group which includes, for example, phenyl, naphthyl (said naphthyl includes α-naphthyl, and β-naphthyl), and fluorenyl (said fluorenyl includes 1-fluorenyl, 2-fluorenyl, 3-fluorenyl, 4-fluorenyl, and 9-fluorenyl). Each group may have at most 5 substituents (said substituents may, for example, be a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a

thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

The C_4-C_{12} heterocyclic aromatic group includes, for example, furyl (said furyl includes 2-furyl, and 3-furyl), thienyl (said thienyl includes 2-thienyl, and 3-thienyl), pyrrolyl (said pyrrolyl includes 1-pyrrolyl, 2-pyrrolyl, and 3-pyrrolyl), oxazolyl (said oxazolyl includes 2-oxazolyl, 4-oxazolyl, and 5-oxazolyl), thiazolyl (said thiazolyl includes 2-thiazolyl, 4-thiazolyl, and 5-thiazolyl), isoxazolyl (said isoxazolyl includes 3-isoxazolyl, 4-isoxazolyl, and 5-isoxazolyl), isothiazolyl (said isothiazolyl includes 3-isothiazolyl, 4-isothiazolyl, and 5-isothiazolyl), furazanyl (said furazanyl includes 3-furazanyl), pyrazolyl (said pyrazolyl includes 1-pyrazolyl, 3-pyrazolyl, and 4-pyrazolyl), oxopyrazolyl (said oxopyrazolyl includes 3-oxopyrazol-1-yl, 3-oxopyrazol-2-yl, 3-oxopyrazol-3-yl, 3-oxopyrazol-4-yl, and 4-oxopyrazol-3-yl), imidazolyl (said imidazolyl includes 1-imidazolyl, 2-imidazolyl, and 4-imidazolyl), oxoimidazolyl (said oxoimidazolyl includes 2-oxoimidazol-1-yl, and 2-oxoimidazol-4-yl), triazolyl (said triazolyl includes 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, and 1,2,4-triazol-4-yl), triazolonyl (said triazolonyl includes 1,2,4(2H,4H)-triazol-3-on-2-yl, 1,2,4-(2H,4H)-triazol-3-on-4-yl, 1,2,4(2H,4H)-triazol-3-on-5-yl, 1,2,4(1H,2H)-triazol-3-on-1-yl,

1,2,4(1H,2H)-triazol-3-on-2-yl, and 1,2,4(1H,2H)-triazol-3-on-5-yl), tetrazolyl (said tetrazolyl includes 1-tetrazolyl, 2-tetrazolyl, and 5-tetrazolyl), pyranyl (said pyranyl includes 2-pyranyl, 3-pyranyl, and 4-pyranyl), pyridyl (said pyridyl includes 2-pyridyl, 3-pyridyl, and 4-pyridyl), pyridonyl (said pyridonyl includes 2-pyridon-1-yl, 2-pyridon-3-yl, 2-pyridon-4-yl, 2-pyridon-5-yl, 2-pyridon-6-yl, 4-pyridon-1-yl, 4-pyridon-2-yl, and 4-pyridon-3-yl), pyridazinyl (said pyridazinyl includes 3-pyridazinyl, and 4-pyridazinyl), pyridazinonyl (said pyridazinonyl includes 3(2H)-pyridazinon-2-yl, 3(2H)-pyridazinon-4-yl, 3(2H)-pyridazinon-5-yl, 3(2H)-pyridazinon-6-yl, 4(1H)-pyridazinon-1-yl, 4(1H)-pyridazinon-3-yl, 4(1H)-pyridazinon-5-yl, and 4(1H)-pyridazinon-6-yl), pyrimidinyl (said pyrimidinyl includes 2-pyrimidinyl, 4-pyrimidinyl, and 5-pyrimidinyl), pyrimidinonyl (said pyrimidinonyl includes (2(1H)-pyrimidinon-1-yl, 2(1H)-pyrimidinon-4-yl, 2(1H)-pyrimidinon-5-yl, 2(1H)-pyrimidinon-6-yl, 4(3H)-pyrimidinon-2-yl, 4(3H)-pyrimidinon-3-yl, 4(3H)-pyrimidinon-5-yl, 4(3H)-pyrimidinon-6-yl, 4(1H)-pyrimidinon-1-yl, 4(1H)-pyrimidinon-2-yl, 4(1H)-pyrimidinon-5-yl, and 4(1H)-pyrimidinon-6-yl), pyrazinyl (said pyrazinyl includes 2-pyrazinyl, 2(1H)-pyrazin-1-yl, 2(1H)-pyrazin-3-yl, 2(1H)-pyrazin-5-yl, and 2(1H)-pyrazin-6-yl), triazinyl (said triazinyl includes 1,2,3-triazin-4-yl, 1,2,3-triazin-5-

yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, and 1,2,4-triazin-6-yl), tetrazinyl (said tetrazinyl includes 1,2,3,4-tetrazin-5-yl, and 1,2,4,5-tetrazin-3-yl), indolyl (said indolyl includes 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, and 7-indolyl), quinolyl (said quinolyl includes 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, and 8-quinolyl), quinolonyl (said quinolonyl includes 2-quinolon-1-yl, 2-quinolon-3-yl, 2-quinolon-4-yl, 2-quinolon-5-yl, 2-quinolon-6-yl, 2-quinolon-7-yl, 2-quinolon-8-yl, 4-quinolon-1-yl, 4-quinolon-2-yl, 4-quinolon-3-yl, 4-quinolon-5-yl, 4-quinolon-6-yl, 4-quinolon-7-yl, and 4-quinolon-8-yl), benzofuranyl (said benzofuranyl includes 2-benzofuranyl, 3-benzofuranyl, 4-benzofuranyl, 5-benzofuranyl, 6-benzofuranyl, and 7-benzofuranyl), benzothienyl (said benzothienyl includes 2-benzothienyl, 3-benzothienyl, 4-benzothienyl, 5-benzothienyl, 6-benzothienyl, and 7-benzothienyl), isoquinolyl (said isoquinolyl includes 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, and 8-isoquinolyl), isoquinolonyl (said isoquinolonyl includes 1-isoquinolon-2-yl, 1-isoquinolon-3-yl, 1-isoquinolon-4-yl, 1-isoquinolon-5-yl, 1-isoquinolon-6-yl, 1-isoquinolon-7-yl, 1-isoquinolon-8-yl, 3-isoquinolon-2-yl, 3-isoquinolon-4-yl, 3-isoquinolon-5-yl, 3-isoquinolon-6-yl, 3-isoquinolon-7-yl, and 3-isoquinolon-8-yl), benzoxazolyl (said benzoxazolyl

includes 2-benzoxazolyl, 4-benzoxazolyl, 5-benzoxazolyl, 6-benzoxazolyl, and 7-benzoxazolyl), benzothiazolyl (said benzothiazolyl includes 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, and 7-benzothiazolyl), benzopyrazolyl (said benzopyrazolyl includes 1-benzopyrazolyl, 2-benzopyrazolyl, 3-benzopyrazolyl, 4-benzopyrazolyl, 5-benzopyrazolyl, 6-benzopyrazolyl, and 7-benzopyrazolyl), benzimidazolyl (said benzimidazolyl includes 1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, and 5-benzimidazolyl), benzotriazolyl (said benzotriazolyl includes 1-benzotriazolyl, 4-benzotriazolyl, and 5-benzotriazolyl), benzopyranyl (said benzopyranyl includes 2-benzopyranyl, 3-benzopyranyl, 4-benzopyranyl, 5-benzopyranyl, 6-benzopyranyl, 7-benzopyranyl, and 8-benzopyranyl), indolizinyl (said indolizinyl includes 1-indolizinyl, 2-indolizinyl, 3-indolizinyl, 5-indolizinyl, 6-indolizinyl, 7-indolizinyl, and 8-indolizinyl), purinyl (said purinyl includes 2-purinyl, 6-purinyl, 7-purinyl, and 8-purinyl), phthalazinyl (said phthalazinyl includes 1-phthalazinyl, 5-phthalazinyl, and 6-phthalazinyl), oxophthalazinyl (said oxophthalazinyl includes 1-oxophthalazin-2-yl, 1-oxophthalazin-4-yl, 1-oxophthalazin-5-yl, 1-oxophthalazin-6-yl, 1-oxophthalazin-7-yl, and 1-oxophthalazin-8-yl), naphthyridinyl (said naphthyridinyl includes 2-naphthyridinyl, 3-naphthyridinyl, and 4-naphthyridinyl), quinoxalinyl (said quinoxalinyl includes

2-quinoxalinyl, 5-quinoxalinyl, and 6-quinoxalinyl), quinazolinyl (said quinazolinyl includes 2-quinazolinyl, 4-quinazolinyl, 5-quinazolinyl, 6-quinazolinyl, 7-quinazolinyl, and 8-quinazolinyl), cinnolinyl (said cinnolinyl includes 3-cinnolinyl, 4-cinnolinyl, 5-cinnolinyl, 6-cinnolinyl, 7-cinnolinyl, and 8-cinnolinyl), benzodioxanyl (said benzodioxanyl includes 1,4-benzodioxan-2-yl, 1,4-benzodioxan-5-yl, and 1,4-benzodioxan-6-yl), oxonaphthalenyl (said oxonaphthalenyl includes 1,4-oxonaphthalen-2-yl, 1,4-oxonaphthalen-5-yl, and 1,4-oxonaphthalen-6-yl), 2,3-dihydrobenzofuranyl (said 2,3-dihydrobenzofuranyl includes 2,3-dihydro-4-benzofuranyl, 2,3-dihydro-5-benzofuranyl, 2,3-dihydro-6-benzofuranyl, and 2,3-dihydro-7-benzofuranyl), benzothiazinyl (said benzothiazinyl includes 1,4-benzothiazin-2-yl, 1,4-benzothiazin-3-yl, 1,4-benzothiazin-4-yl, 1,4-benzothiazin-5-yl, 1,4-benzothiazin-6-yl, 1,4-benzothiazin-7-yl, and 1,4-benzothiazin-8-yl), pteridinyl (said pteridinyl includes 2-pteridinyl, 4-pteridinyl, 6-pteridinyl, and 7-pteridinyl), pyrazolo[1,5-a]pyrimidinyl (said pyrazolo[1,5-a]pyrimidinyl includes pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-3-yl, pyrazolo[1,5-a]pyrimidin-5-yl, pyrazolo[1,5-a]pyrimidin-6-yl, and pyrazolo[1,5-a]pyrimidin-7-yl), pyrazolo[5,1-c][1,2,4]triazinyl (said pyrazolo[5,1-c][1,2,4]triazinyl includes pyrazolo[5,1-c][1,2,4]triazin-3-yl,

pyrazolo[5,1-c][1,2,4]triazin-4-yl, pyrazolo[5,1-c][1,2,4]triazin-7-yl, and pyrazolo[5,1-c][1,2,4]triazin-8-yl), thiazolo[3,2-b]triazolyl (said thiazolo[3,2-b]triazolyl includes thiazolo[3,2-b]triazol-2-yl, thiazolo[3,2-b]triazol-5-yl, and thiazolo[3,2-b]triazol-6-yl), benzopyrano[2,3-b]pyridyl (said benzopyrano[2,3-b]pyridyl includes benzopyrano[2,3-b]pyridin-2-yl, benzopyrano[2,3-b]pyridin-3-yl, benzopyrano[2,3-b]pyridin-4-yl, benzopyrano[2,3-b]pyridin-5-yl, benzopyrano[2,3-b]pyridin-6-yl, benzopyrano[2,3-b]pyridin-7-yl, benzopyrano[2,3-b]pyridin-8-yl, and benzopyrano[2,3-b]pyridin-9-yl), 5H-benzopyrano[2,3-b]pyridonyl (said 5H-benzopyrano[2,3-b]pyridonyl includes 5H-benzopyrano[2,3-b]pyridin-5-on-2-yl, 5H-benzopyrano[2,3-b]pyridin-5-on-3-yl, 5H-benzopyrano[2,3-b]pyridin-5-on-4-yl, 5H-benzopyrano[2,3-b]pyridin-5-on-6-yl, 5H-benzopyrano[2,3-b]pyridin-5-on-7-yl, and 5H-benzopyrano[2,3-b]pyridin-5-on-8-yl), xanthenyl (said xanthenyl includes 1-xanthenyl, 2-xanthenyl, 3-xanthenyl, 4-xanthenyl, and 9-xanthenyl), phenoxathiinyl (said phenoxathiinyl includes 1-phenoxathiinyl, 2-phenoxathiinyl, 3-phenoxathiinyl, and 4-phenoxathiinyl), carbazolyl (said carbazolyl includes 1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl, and 9-carbazolyl), acridinyl (said acridinyl includes 1-acridinyl, 2-acridinyl, 3-acridinyl, 4-acridinyl, and 9-acridinyl), phenazinyl (said phenazinyl includes 1-

phenazinyl, 2-phenazinyl, 3-phenazinyl, and 4-phenazinyl), phenothiazinyl (said phenothiazinyl includes 1-phenothiazinyl, 2-phenothiazinyl, 3-phenothiazinyl, 4-phenothiazinyl, and 10-phenothiazinyl), phenoxazinyl (said phenoxazinyl includes 1-phenoxazinyl, 2-phenoxazinyl, 3-phenoxazinyl, 4-phenoxazinyl, and 10-phenoxazinyl), and thianthrenyl (said thianthrenyl includes 1-thianthrenyl, 2-thianthrenyl, 3-thianthrenyl, 4-thianthrenyl, 6-thianthrenyl, 7-thianthrenyl, 8-thianthrenyl, and 9-thianthrenyl). Preferred examples of the C_4-C_{12} heterocyclic aromatic group include furyl (said furyl includes 2-furyl, and 3-furyl), thienyl (said thienyl includes 2-thienyl, and 3-thienyl), pyrrolyl (said pyrrolyl includes 1-pyrrolyl, 2-pyrrolyl, and 3-pyrrolyl), oxazolyl (said oxazolyl includes 2-oxazolyl, 4-oxazolyl, and 5-oxazolyl), thiazolyl (said thiazolyl includes 2-thiazolyl, 4-thiazolyl, and 5-thiazolyl), isoxazolyl (said isoxazolyl includes 3-isoxazolyl, 4-isoxazolyl, and 5-isoxazolyl), isothiazolyl (said isothiazolyl includes 3-isothiazolyl, 4-isothiazolyl, and 5-isothiazolyl), imidazolyl (said imidazolyl includes 1-imidazolyl, 2-imidazolyl, and 4-imidazolyl), pyridyl (said pyridyl includes 2-pyridyl, 3-pyridyl, and 4-pyridyl), pyridazinyl (said pyridazinyl includes 3-pyridazinyl, and 4-pyridazinyl), pyridazinonyl (said pyridazinonyl includes 3(2H)-pyridazinon-2-yl, 3(2H)-pyridazinon-4-yl, 3(2H)-pyridazinon-5-yl, and 3(2H)-

pyridazinon-6-yl), pyrimidinyl (said pyrimidinyl includes 2-pyrimidinyl, 4-pyrimidinyl, and 5-pyrimidinyl), pyrazinyl (said pyrazinyl includes 2-pyrazinyl), indolyl (said indolyl includes 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, and 7-indolyl), quinolyl (said quinolyl includes 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, and 8-quinolyl), benzoxazolyl (said benzoxazolyl includes 2-benzoxazolyl, 4-benzoxazolyl, 5-benzoxazolyl, 6-benzoxazolyl, and 7-benzoxazolyl), benzothiazolyl (said benzothiazolyl includes 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, and 7-benzothiazolyl), benzimidazolyl (said benzimidazolyl includes 1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, and 5-benzimidazolyl), phthalazinyl (said phthalazinyl includes 1-phthalazinyl, 5-phthalazinyl, and 6-phthalazinyl), quinoxalinyl (said quinoxalinyl includes 2-quinoxalinyl, 5-quinoxalinyl, and 6-quinoxalinyl), benzothiazinyl (said benzothiazinyl includes 1,4-benzothiazin-2-yl, 1,4-benzothiazin-3-yl, 1,4-benzothiazin-4-yl, 1,4-benzothiazin-5-yl, 1,4-benzothiazin-6-yl, 1,4-benzothiazin-7-yl, and 1,4-benzothiazin-8-yl), pyrazolo[1,5-a]pyrimidinyl (said pyrazolo[1,5-a]pyrimidinyl includes pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-3-yl, pyrazolo[1,5-a]pyrimidin-5-yl, pyrazolo[1,5-a]pyrimidin-6-yl, and pyrazolo[1,5-a]pyrimidin-7-yl), pyrazolo[5,1-

c][1,2,4]triazinyl (said pyrazolo[5,1-c][1,2,4]triazinyl includes pyrazolo[5,1-c][1,2,4]triazin-3-yl, pyrazolo[5,1-c][1,2,4]triazin-4-yl, pyrazolo[5,1-c][1,2,4]triazin-7-yl, and pyrazolo[5,1-c][1,2,4]triazin-8-yl), thiazolo[3,2-b]triazolyl (said thiazolo[3,2-b]triazolyl includes thiazolo[3,2-b]triazol-2-yl, thiazolo[3,2-b]triazol-5-yl, and thiazolo[3,2-b]triazol-6-yl), and benzopyrano[2,3-b]pyridyl (said benzopyrano[2,3-b]pyridyl includes benzopyrano[2,3-b]pyridin-2-yl, benzopyrano[2,3-b]pyridin-3-yl, benzopyrano[2,3-b]pyridin-4-yl, benzopyrano[2,3-b]pyridin-5-yl, benzopyrano[2,3-b]pyridin-6-yl, benzopyrano[2,3-b]pyridin-7-yl, benzopyrano[2,3-b]pyridin-8-yl, and benzopyrano[2,3-b]pyridin-9-yl). Each group may have at most 5 substituents (said substituents may, for example, be a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl

or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

The C_4-C_6 heterocycloaliphatic group includes, for example, piperidyl (said piperidyl includes 1-piperidyl, 2-piperidyl, 3-piperidyl, and 4-piperidyl), pyrrolidinyl (said pyrrolidinyl includes 1-pyrrolidinyl, 2-pyrrolidinyl, and 3-pyrrolidinyl), imidazolidinyl (said imidazolidinyl includes 1-imidazolidinyl, 2-imidazolidinyl, and 4-imidazolidinyl), pyrazolidinyl (said pyrazolidinyl includes 1-pyrazolidinyl, 3-pyrazolidinyl, and 4-pyrazolidinyl), morpholinyl (said morpholinyl includes 2-morpholinyl, 3-morpholinyl, and 4-morpholinyl), and tetrahydrofuranyl (said tetrahydrofuranyl includes 2-tetrahydrofuranyl, and 3-tetrahydrofuranyl). Each group may have at most 5 substituents (said substituents may, for example, be a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a

hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

In the definitions of R^a, R^b and R^c:

The C_1-C_7 alkyl group includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl, and n-heptyl. Preferred are methyl, ethyl and n-propyl. Each group may be substituted with a hydroxyl group.

The C_3-C_7 cycloalkyl group includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl, and

bicyclo[3.1.1]heptyl. Preferred are cyclopropyl and cyclohexyl. Each group may be substituted by a hydroxyl group.

The C_3-C_7 cycloalkenyl group includes, for example, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, cyclopentadienyl, 2-bicyclo[2.2.1]heptenyl and 2,5-bicyclo[2.2.1]heptadienyl. Each group may be substituted by a hydroxyl group.

The C_1-C_7 alkoxy group includes, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy and heptyloxy.

The C_1-C_7 alkylthio group includes, for example, methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, s-buthylthio, t-butylthio, pentylthio, hexylthio and heptylthio.

The naphthyl group includes an α-naphthyl group, a β-naphthyl group. The furanyl group includes a 2-furanyl group and a 3-furanyl group. The thienyl group includes a 2-thienyl group and a 3-thienyl group. The imidazolyl group includes a 1-imidazolyl group, a 2-imidazolyl group and a 4-imidazolyl group. The pyridyl group includes a 2-pyridyl group and a 3-pyridyl group and a 4-pyridyl group. Each groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a

fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group.

The phenyl and the benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group.

The C_1-C_3 alkoxycarbonyl group includes, for example, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl and i-propoxycarbonyl.

The halogen atom includes a fluorine atom, a chlorine atom, a bromine atom and an iodine atom. Preferred are a fluorine atom, a chlorine atom and a bromine atom.

Each of R^2 and R^3 independently is a hydrogen atom, a C_1-C_7 alkyl group (which may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl or n-heptyl, preferably methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl, and said C_1-C_7 alkyl group may be substituted with at most two hydroxyl groups, preferably one hydroxyl group), a C_3-C_7 cycloalkyl group (which may, for example, be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl or bicyclo[3.1.1]heptyl, preferably cyclopropyl or cyclohexyl, and said C_3-C_7 cycloalkyl group may be substituted with at most 2 hydroxyl group, preferably one

hydroxyl group), a naphthyl group (which may be an α-naphthyl group, or a β-naphthyl group), a benzyl group, a pyridyl group (which may, for example, be a 2-pyridyl group, a 3-pyridyl group or a 4-pyridyl group, preferably a 2-pyridyl group), a pyrimidinyl group (which may, for example, be a 2-pyrimidinyl group, a 4-pyrimidinyl group or a 5-pyrimidinyl group), a pyridazinyl group (which may, for example, be a 3-pyridazinyl group or a 4-pyridazinyl group), a furanyl group (which may, for example, be a 2-furanyl group or a 3-furanyl group), a thienyl group (which may, for example, be a 2-thienyl group or a 3-thienyl group), a pyrrolyl group (which may, for example, be a 1-pyrrolyl group, a 2-pyrrolyl group or a 3-pyrrolyl group), a pyrazolyl group (which may, for example, be a 1-pyrazolyl group, a 3-pyrazolyl group or a 4-pyrazolyl group), an imidazolyl group (which may, for example, be a 1-imidazolyl group, a 2-imidazolyl group or a 4-imidazolyl group), a pyranyl group (which may, for example, be 2-pyranyl, 3-pyranyl or 4-pyranyl, preferably 2-pyranyl), a quinolyl group (which may, for example, be 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl or 8-quinolyl, preferably 2-quinolyl), a bezoxazolyl group (which may, for example, be a 2-benzoxalyl group, a 4-benzoxazolyl group, a 5-benzoxazolyl group, a 6-benzoxazolyl group or a 7-benzoxazolyl group, preferably a 2-benzoxazolyl group), a benzothiazolyl group (which may, for example, be a 2-

benzothiazolyl group, a 4-benzothiazolyl group, a 5-benzothiazolyl group, a 6-benzothiazolyl group or a 7-benzothiazolyl group, preferably a 2-benzothiazolyl group), or a benzimidazolyl group (which may, for example, be a 1-benzimidazolyl group, a 2-benzimidazolyl group, a 4-benzimidazolyl group or a 5-benzimidazolyl group, preferably a 2-benzimidazolyl group).

The halogen atom in a case where R^2 and R^3 are bonded to a carbon atom at the 3-, 4- or 5-position of the pyrazole ring, may be a fluorine atom, a chlorine atom, a bromine atom or an iodine atom, preferably a fluorine atom, a chlorine atom or a bromine atom, more preferably a chlorine atom or a bromine atom.

When R^2 or R^3 is a phenyl, naphthyl, benzyl, pyridyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyranyl, quinolyl, benzoxazolyl, benzothiazolyl, or benzimidazolyl group, the substituents for such a phenyl, naphthyl, benzyl, pyridyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyranyl, quinolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl group may be as follows.

The C_1-C_7 alkyl group includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl and n-heptyl. Preferred may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl.

The C_1-C_7 alkoxy group includes, for example,

methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy and heptyloxy. Preferred may, for example, be methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy or t-butoxy.

The halogen atom may, for example, be a fluorine atom, a chlorine atom, a bromine atom or an iodine atom, preferably, a fluorine atom, a chlorine atom or a bromine atom.

R^2 and R^3 are preferably bonded on the nitrogen atom at the 1-position or on the carbon atom at the 4-position of the pyrazole ring. When R^2 and R^3 are bonded on the carbon atom at the 4-position of the pyrazole ring, each of R^2 and R^3 is more preferably hydrogen, methyl, ethyl, phenyl, fluorine, chlorine or bromine. When R^2 and R^3 are bonded on the nitrogen atom at the 1-position of the pyrazole ring, each of them is more preferably hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl, n-heptyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, α-naphthyl, β-naphthyl, 2-pyridyl or benzyl.

R^4 is a hydrogen atom or a C_1-C_7 alkyl group (which may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl or n-heptyl, preferably methyl), or forms a bond together with R^7. It is preferably a hydrogen atom or a methyl group, or forms a bond together with R^7. More

preferably, it is a hydrogen atom, or forms a bond together with R^7.

R^5 is a hydrogen atom or a carboxymethyl group, preferably a hydrogen atom.

R^6 is a hydrogen atom, a C_1-C_7 alkyl group (which may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl or n-heptyl, preferably methyl) or a C_3-C_7 cycloalkyl group (which may, for example, be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, preferably cyclopropyl). It is preferably a hydrogen atom or methyl, more preferably a hydrogen atom.

R^7 is a hydrogen atom, a C_1-C_7 alkyl group (which may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl or n-heptyl, preferably methyl) or a C_3-C_7 cycloalkyl group (which may, for example, be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, preferably cyclopropyl), or forms a bond together with R^4. It is preferably a hydrogen atom, or forms a bond together with R^4.

X^1 is S or O, preferably S.

X^2 is S, O or NH, preferably O or S, more preferably O.

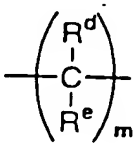
V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or C_1-C_3 alkyl (which may, for example, be methyl, ethyl, n-propyl or i-propyl, preferably methyl)). It is

preferably O, S or NR^8, more preferably O.

W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3, preferably at most 2, of hydroxyl, oxo and C_1-C_7 alkyl groups.

The C_1-C_7 alkyl group includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl and n-heptyl. Preferred may, for example, be methyl.

W is preferably



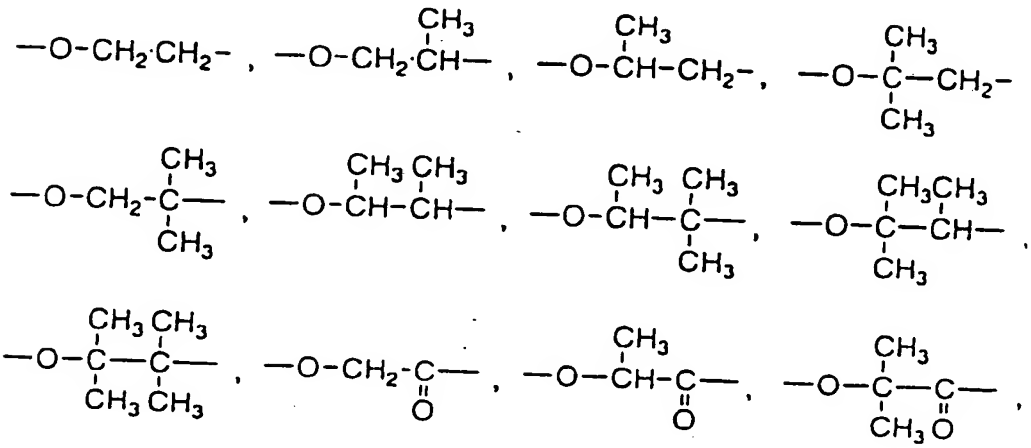
wherein m is from 1 to 5, and each of R^d and R^e is a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond (provided that R^d and R^e on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group).

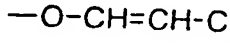
Y is preferably bonded on the carbon atom at the 3- or 5-position of the pyrazole ring, and R^1 is preferably bonded on the carbon atom at the 3-, 4- or 5-position of the pyrazole ring, more preferably on the carbon atom at the 3- or 5-position.

R^1 may be $-V_k-W_1-Z$, -V-W-V-W-Z, -W-V-W-Z, -V-W-V-Z or -W-V-Z in addition to the one mentioned above.

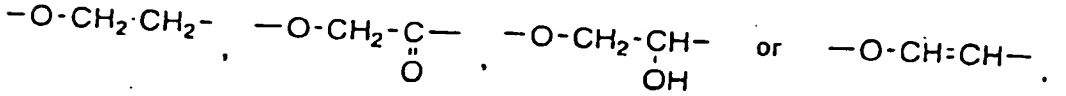
$-V_k-W_1-Z$ may, for example, be -O-W-Z or -W-Z.

Preferably, the above -O-W- may, for example, be

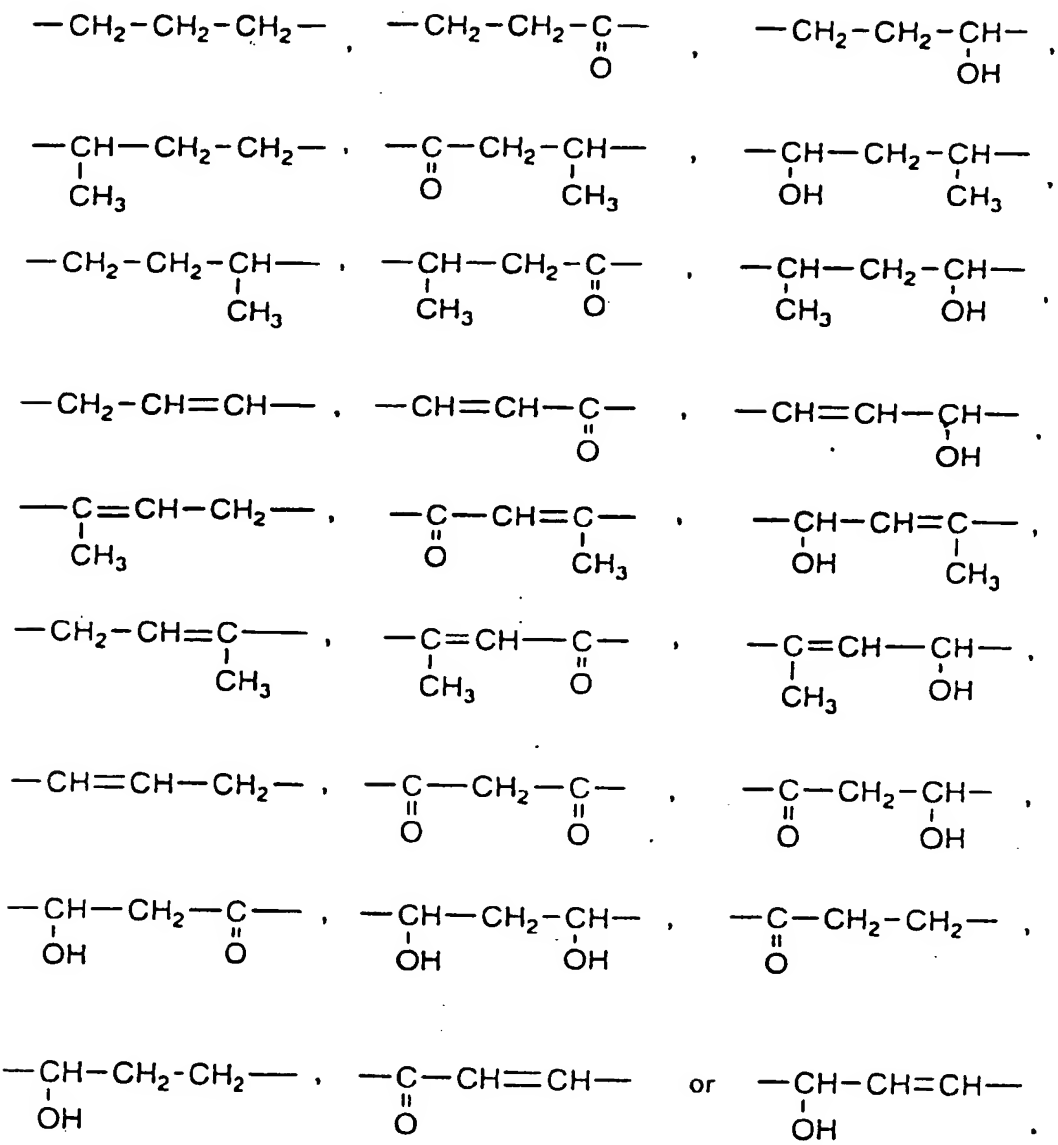


or  .

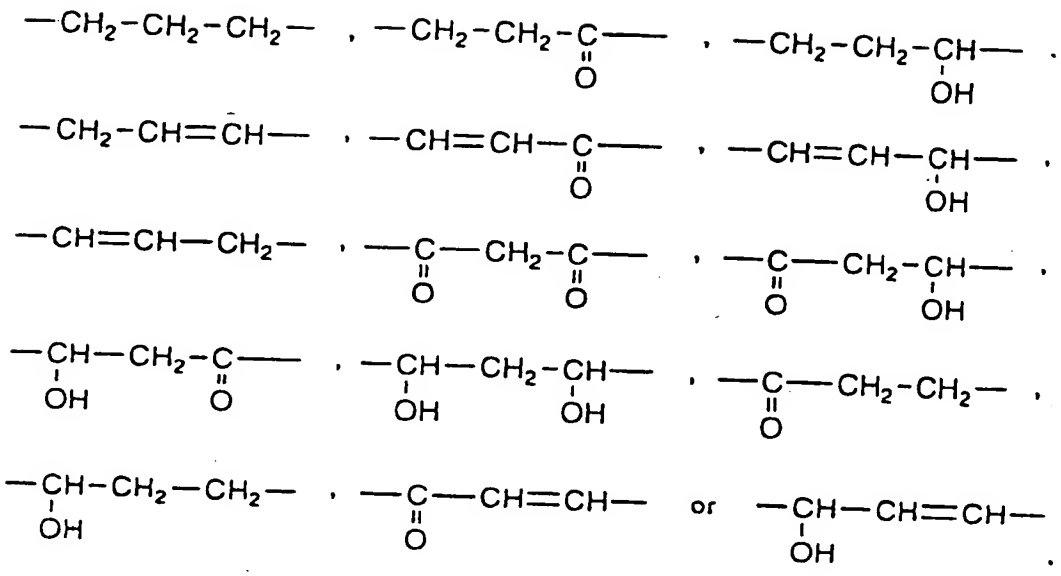
More preferably, it may, for example, be



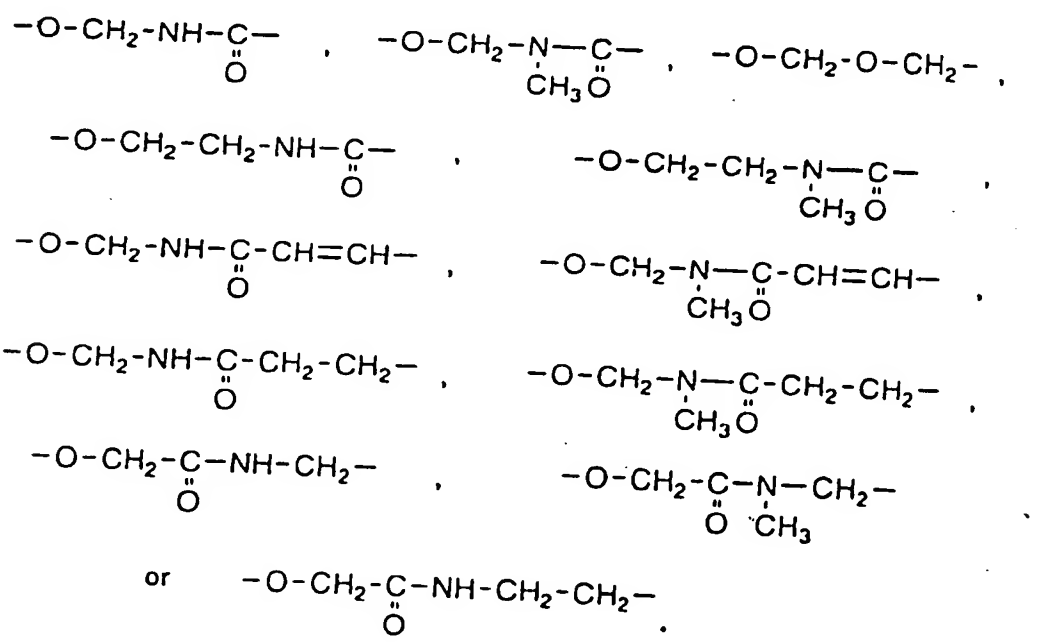
Preferably, -W- may, for example, be



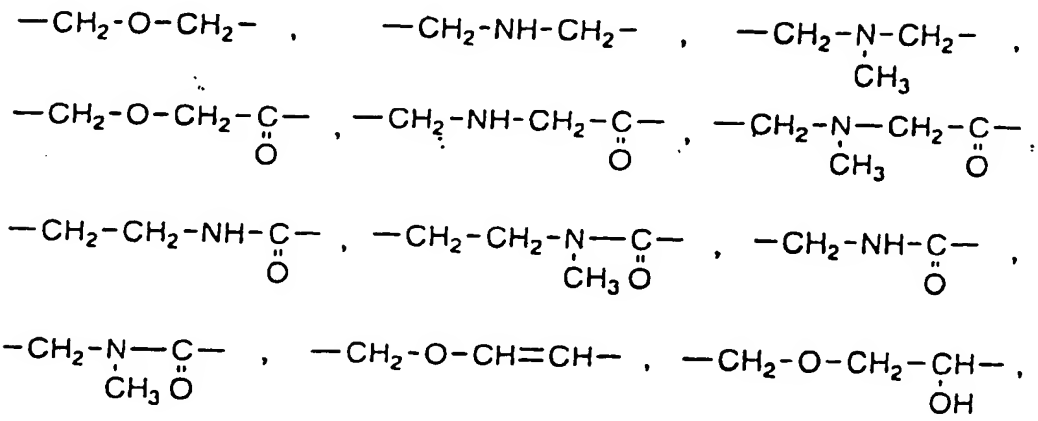
More preferably, it may, for example, be



Preferably, -V-W-V-W-Z may, for example, be -O-W-V-W-Z. More preferably, it may, for example, be

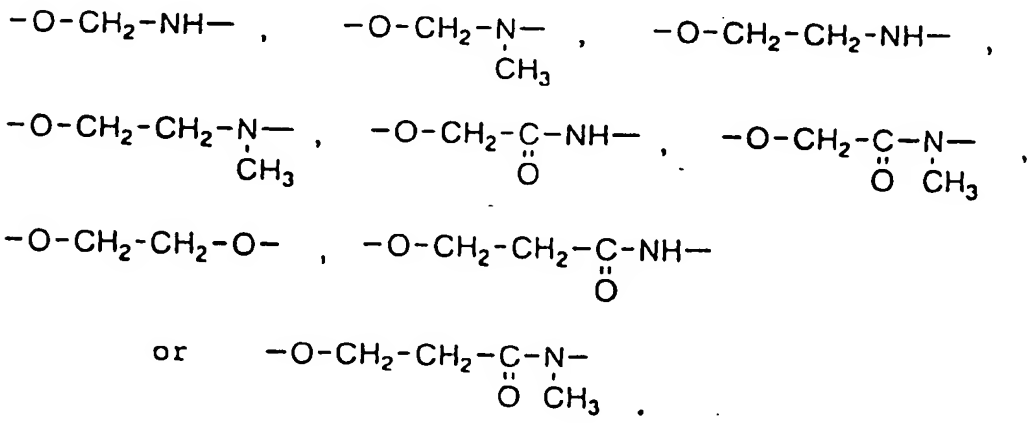


Preferably, -W-V-W-Z may, for example, be

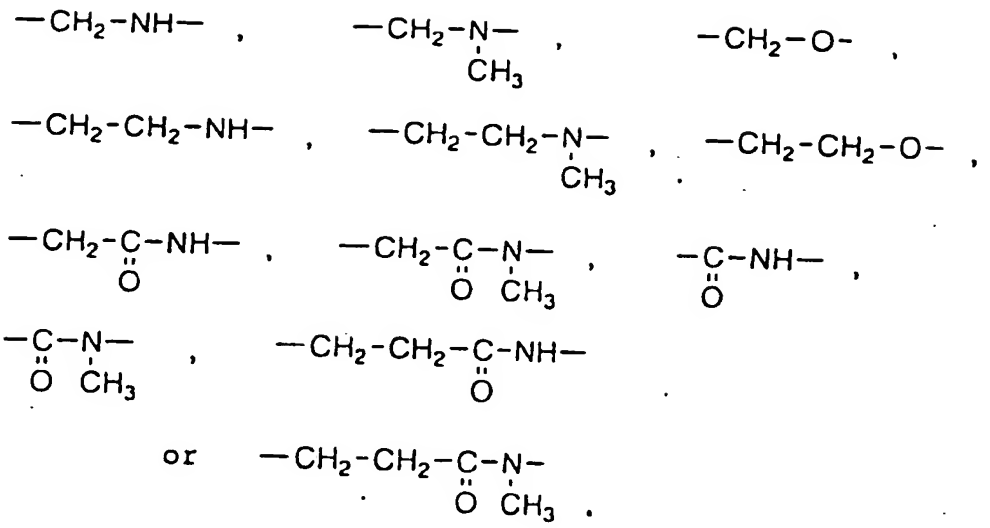


Preferably, -V-W-V-Z may, for example, be -O-W-V-Z.

More preferably, it may, for example, be



Preferably, -W-V may, for example, be

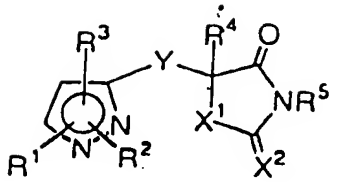


In the present specification, "n" means normal, "i" means iso, "s" means secondary, "t" means tertiary, "c" means cyclo, "Me" means methyl, "Et" means ethyl, "Pr" means propyl, "Bu" means butyl, "Pen" means pentyl, "Hex" means hexyl, "Ph" means phenyl, and "Hal" means halogen.

Among these compounds, there is a compound having an asymmetric carbon atom at the 5-position of thiazolidine ring. The compound having the above formula (I) includes all of these optical isomers and their mixtures.

The following compounds (1) to (23) may be mentioned as preferred examples of the compound of the formula (I) of the present invention.

(1) The pyrazole type thiazolidine compound and its salt of the present invention, wherein the compound of the formula (I) is represented by the following formula (Ia):



(Ia)

wherein R^1 is a C_1-C_{10} alkyl group, a C_2-C_{10} alkenyl group, a C_2-C_{10} alkynyl group, a C_1-C_{10} alkoxy group, a C_2-C_{10} alkenyloxy group, a C_1-C_{10} alkylthio group, a C_1-C_{10} monoalkylamino group or a di-C_1-C_{10} alkylamino group (each of said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyloxy, C_1-C_{10} alkylthio, C_1-C_{10} monoalkylamino and di-C_1-C_{10} alkylamino groups may be substituted with a hydroxyl group or a C_1-C_7 alkyl group), or

$-V_k-W_l-Z$ (among groups of Z as defined for the formula (I), said C_3-C_{10} cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, or adamantyl, said C_3-C_7 cycloalkenyl group is cyclohexenyl, cyclopentadienyl, 2-bicylo[2.2.1]heptenyl or 2,5-bicyclo[2.2.1]heptadienyl, said C_6-C_{14} aromatic group is phenyl, naphthyl, indenyl, indanyl or fluorenyl, said C_4-C_{12} heterocyclic aromatic group is furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, furazanyl, pyrazolyl, oxopyrazolyl, imidazolyl, oxoimidazolyl, triazolyl, triazolonyl, tetrazolyl, pyranyl, pyridyl, pyridonyl, pyridazinyl, pyridazinonyl,

pyrimidinyl, pyrimidinonyl, pyrazinyl, triazinyl, tetrazinyl, indolyl, quinolyl, quinolonyl, benzofuranyl, benzothienyl, isoquinolyl, isoquinolonyl, benzoxazolyl, benzothiazolyl, benzopyrazolyl, benzimidazolyl, benzotriazolyl, benzopyranyl, indolizinyl, purinyl, phthalazinyl, oxophthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzodioxanyl, oxonaphthalenyl, dihydrobenzofuranyl, benzothiazinyl, pteridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[5,1-c][1,2,4]triazinyl, thiazolo[3,2-b]triazolyl, benzopyrano[2,3-b]pyridyl, 5H-benzopyrano[2,3-b]pyridonyl, xanthenyl, phenoxathiinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, or thianthrenyl, and said C_4-C_6 heterocycloaliphatic group is piperidyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, morpholinyl, or tetrahydrofuranyl, (each of said C_3-C_{10} cycloalkyl, C_3-C_7 cycloalkenyl, C_6-C_{14} aromatic, C_4-C_{12} heterocyclic aromatic and C_4-C_6 heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting of a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide

group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group),

W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, and

each of k and ℓ is 0 or 1),

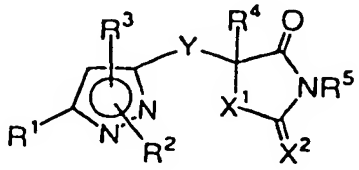
-V-W-V-W-Z (V, W and Z are as defined above, and two V's and W's may, respectively, be the same or different),

-W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different),

-V-W-V-Z (V, W and Z are as defined above, and two V's may be the same or different), or

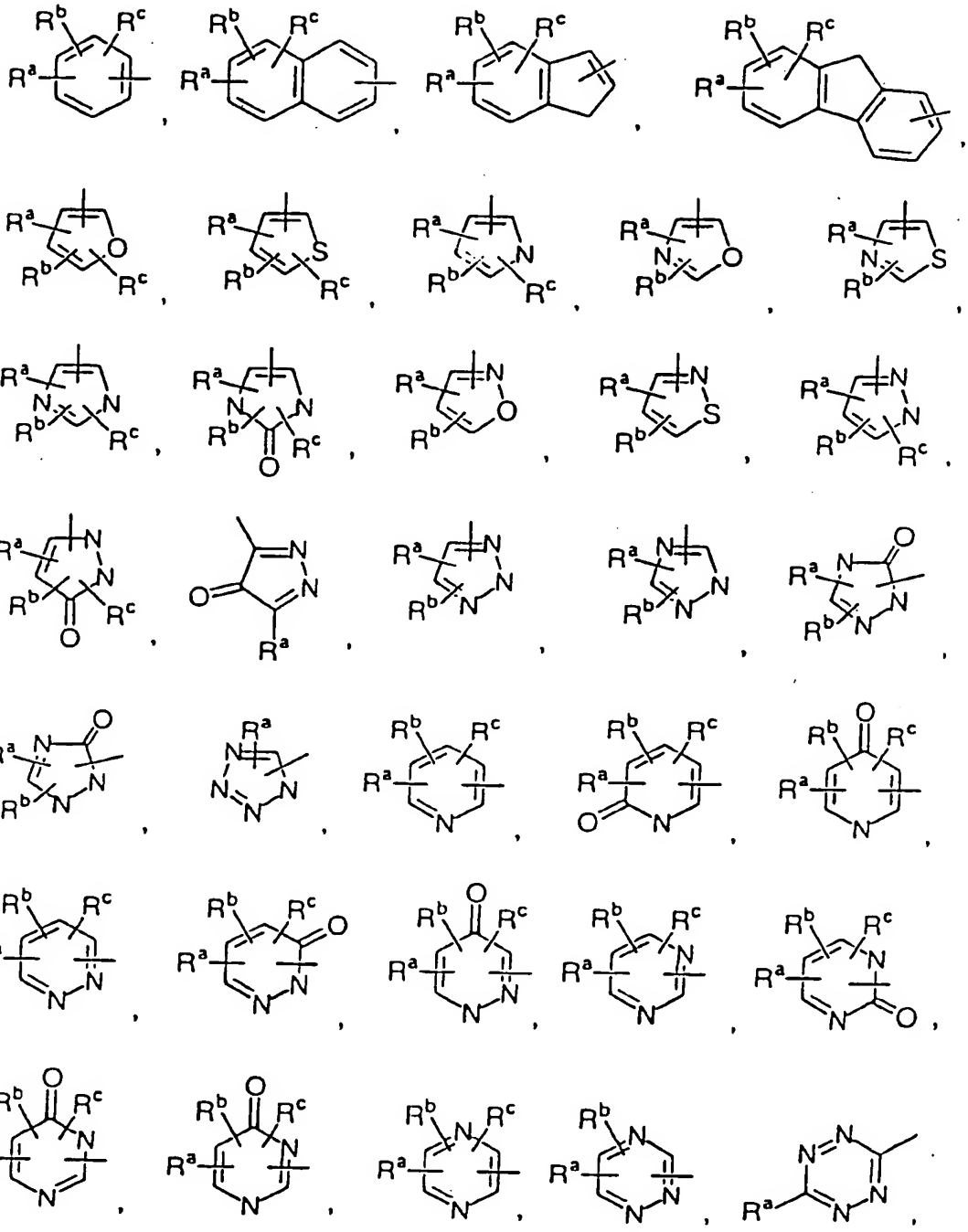
-W-V-Z (V, W and Z are as defined above);

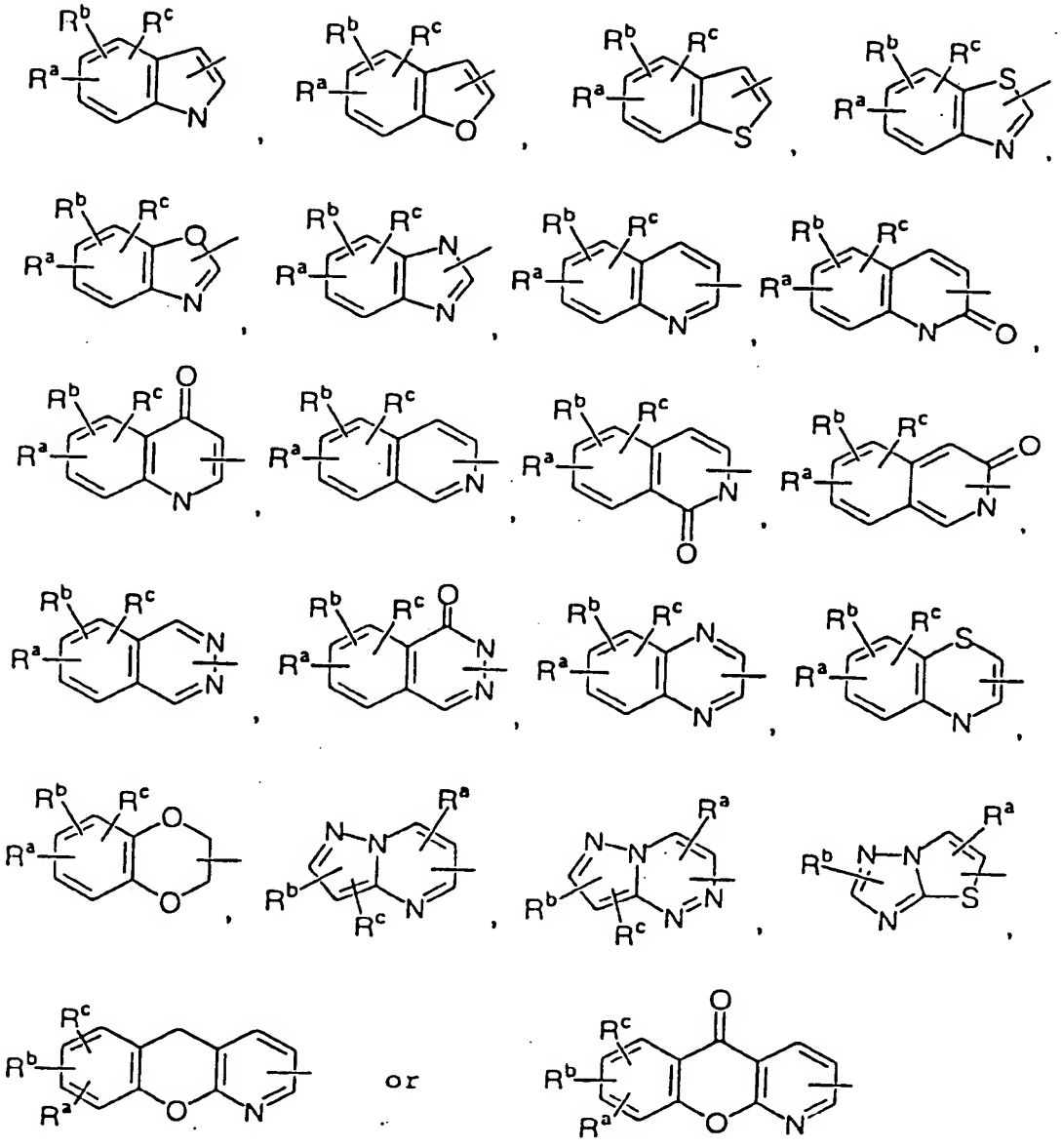
(2) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (1), wherein the compound of the formula (Ia) is represented by the formula (Ib):



(Ib)

(3) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (2), wherein R^1 is -V-W-Z, -W-Z, -V-W-V-W-Z, -W-V-W-Z, -V-W-V-Z or -W-V-Z (V is O, S or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, when two V's or W's are present, such V's or W's may be the same or different, and Z is




or

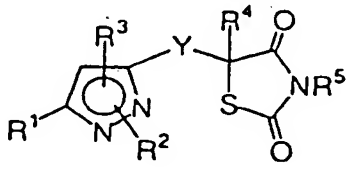
wherein each of R^a and R^b is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group or a hydroxymethyl group);

R^2 or R^3 is a hydrogen atom, a C_1-C_4 alkyl group, a C_3-C_6 cycloalkyl group, a phenyl group, a naphthyl group,

a benzyl group or a pyridyl group, when it is on the nitrogen atom at the 1-position of the pyrazole ring; and

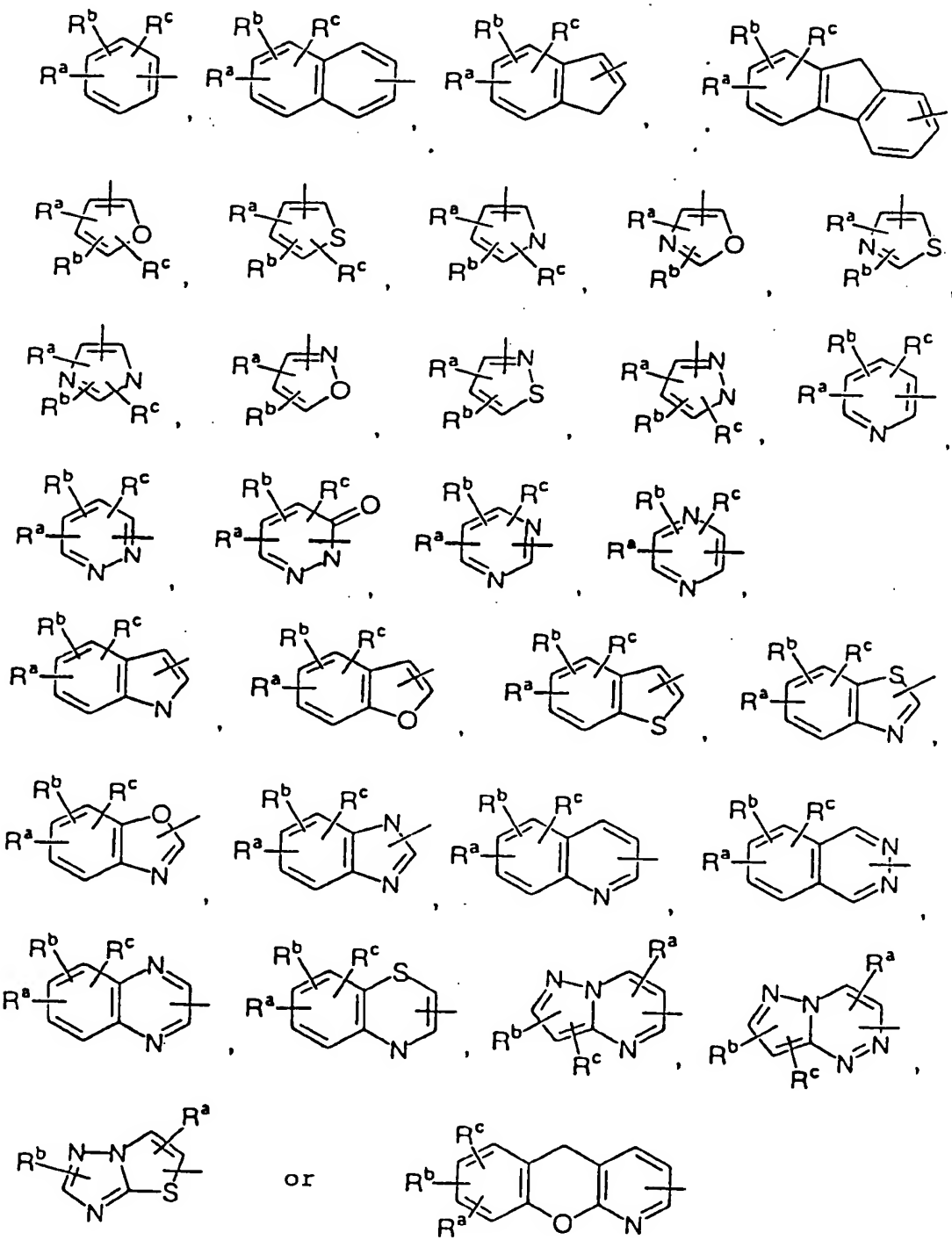
R^2 or R^3 is a hydrogen atom, a C_1-C_4 alkyl group, a phenyl group or a halogen atom, when it is on the carbon atom at the 4-position of the pyrazole ring.

(4) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (3), wherein said compound is represented by the formula:



wherein Y is CR^6R^7 (R^6 is a hydrogen atom or a methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4);

R^1 is -V-W-Z, -W-Z, -V-W-V-W-Z, -W-V-W-Z, -V-W-V-Z or -W-V-Z (V is O, S or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, when two V's or W's are present, such V's or W's may be the same or different, and Z is



wherein each R^a and R^b is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a phenoxy group, a benzyloxy group, a phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group or a hydroxymethyl group);

R^4 is a hydrogen atom or a methyl group, or forms a bond together with R^7;

R^5 is a hydrogen atom or a carboxymethyl group.

(5) The pyrazole type thiazolidine compound and its

salt according to the above-mentioned (4), wherein:

R^1 is -O-W-Z, wherein W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 2 of hydroxyl, oxo and C_1-C_7 alkyl groups (provided that the first carbon atom bonded with the oxygen atom is not substituted with a hydroxyl group or an oxo group).

(6) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (4), wherein:

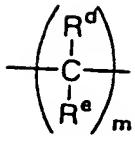
R^1 is -O-W-V-W-Z, -W-V-W-Z, -O-W-V-Z or -W-V-Z, wherein V is O or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 2 of hydroxyl, oxo and C_1-C_7 alkyl groups (provided that the first carbon atom bonded with the oxygen atom is not substituted with a hydroxyl group or an oxo group when two W's are present, such W's may be the same or different).

(7) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (4), wherein:

R^1 is -W-Z, wherein W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 2 hydroxyl, oxo and C_1-C_7 alkyl groups.

(8) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (5), wherein:

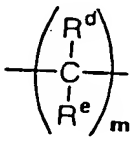
R^1 is -O-W-Z, wherein W is



wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond (provided that R^d and R^e on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group).

(9) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (6), wherein:

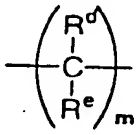
R^1 is -O-W-V-W-Z, -W-V-W-Z, -O-W-V-Z or -W-V-Z, wherein W is



wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond (provided that R^d and R^e on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group).

(10) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (7), wherein:

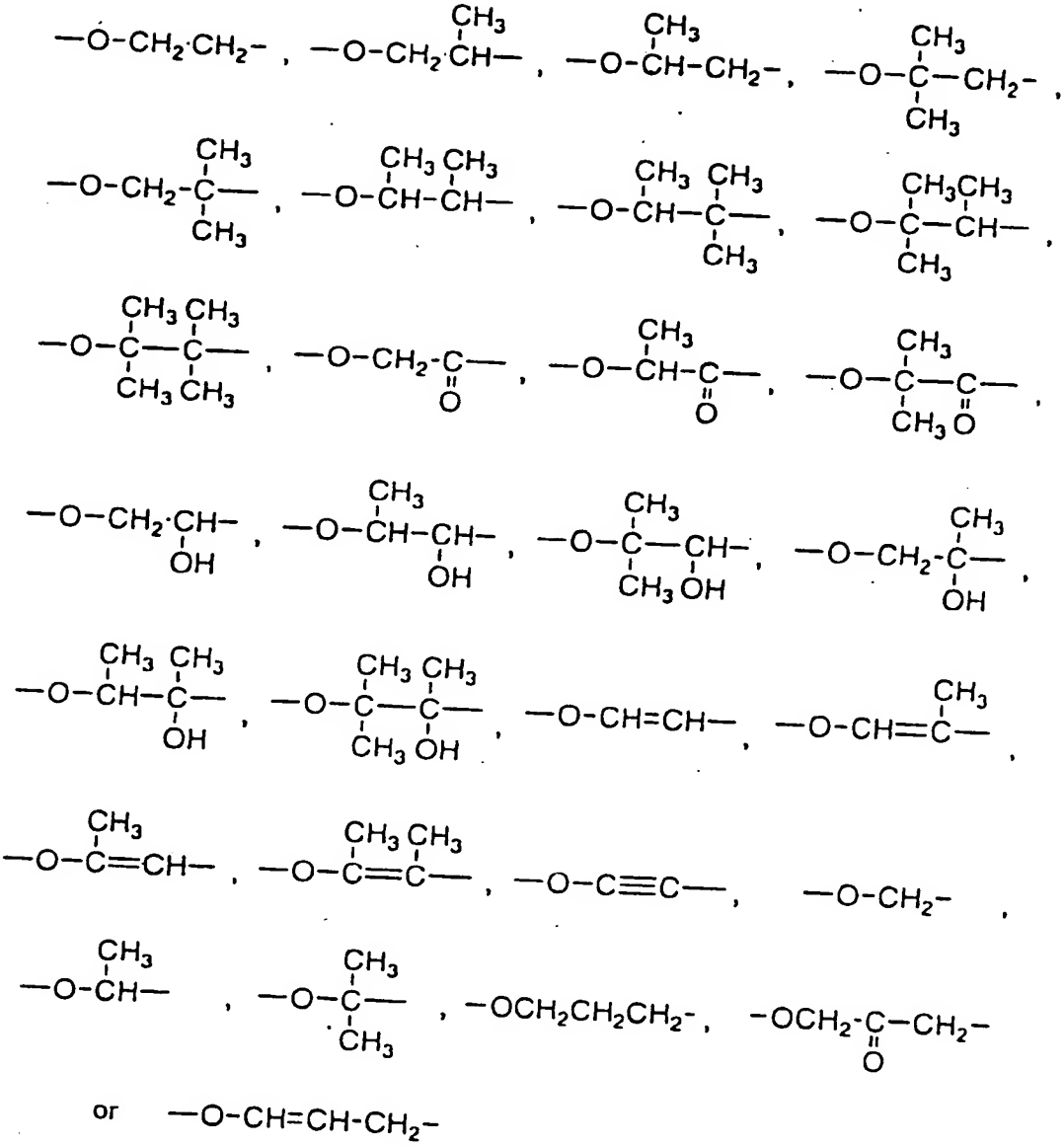
R^1 is -W-Z, wherein W is



wherein m is from 1 to 5, each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond.

(11) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (8), wherein:

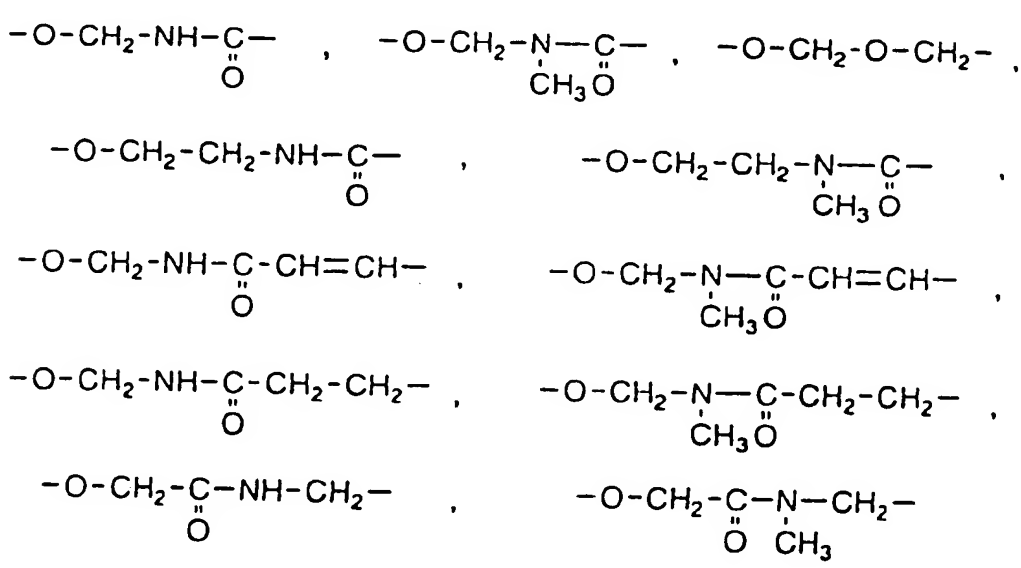
R^1 is -O-W-Z, wherein -O-W- is



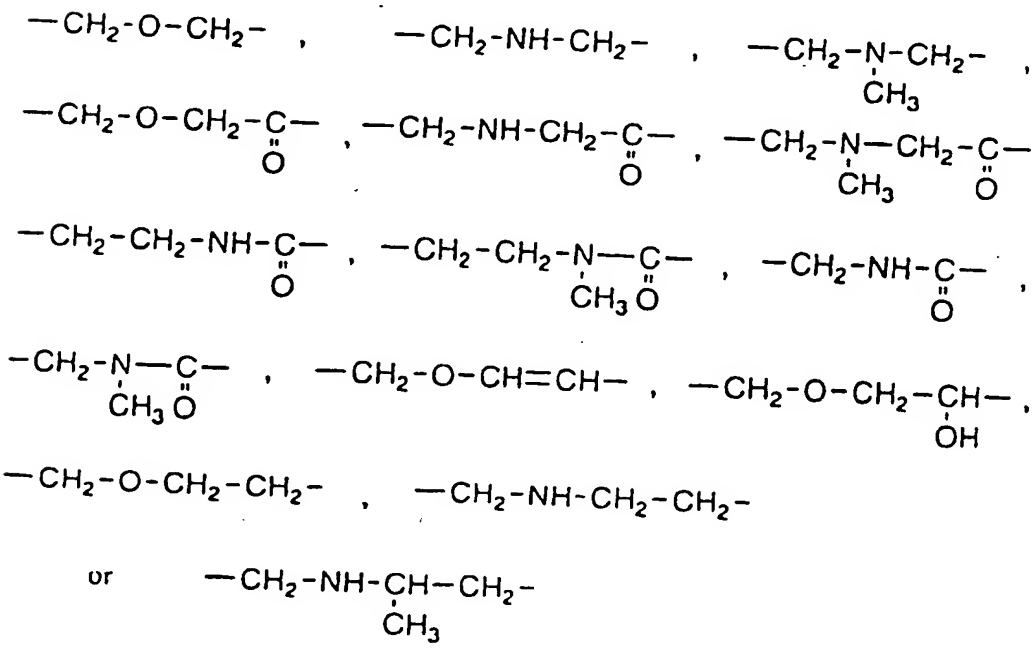
(12) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (9), wherein:

R^1 is -O-W-V-W-Z, -W-V-W-Z, -O-W-V-Z or -W-V-Z,

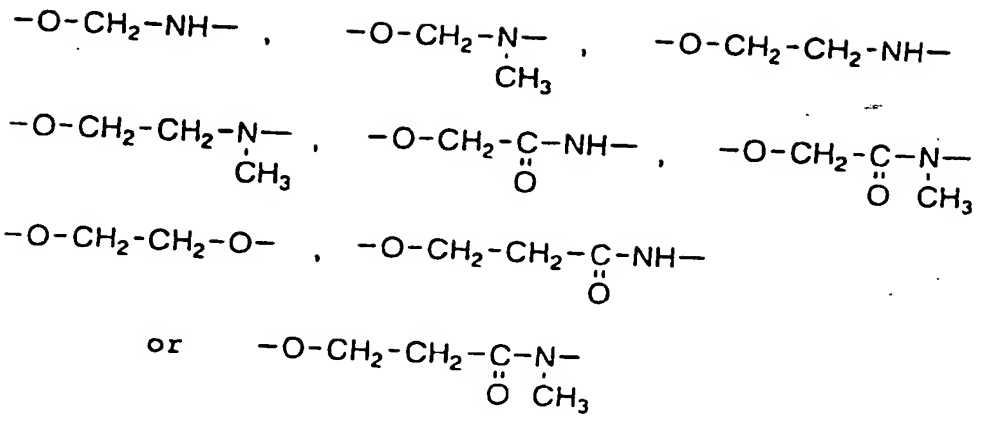
wherein -O-W-V-W- is



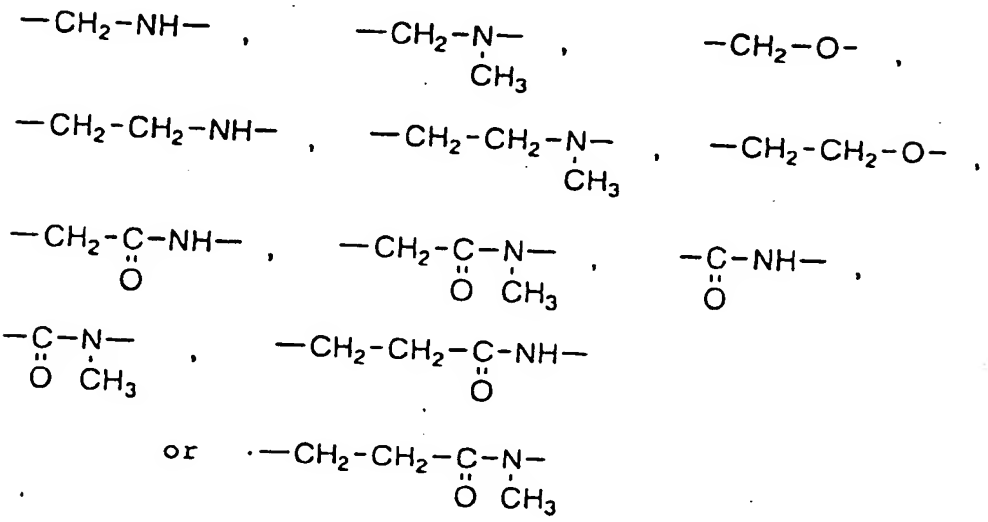
-W-V-W- is



-O-W-V- is

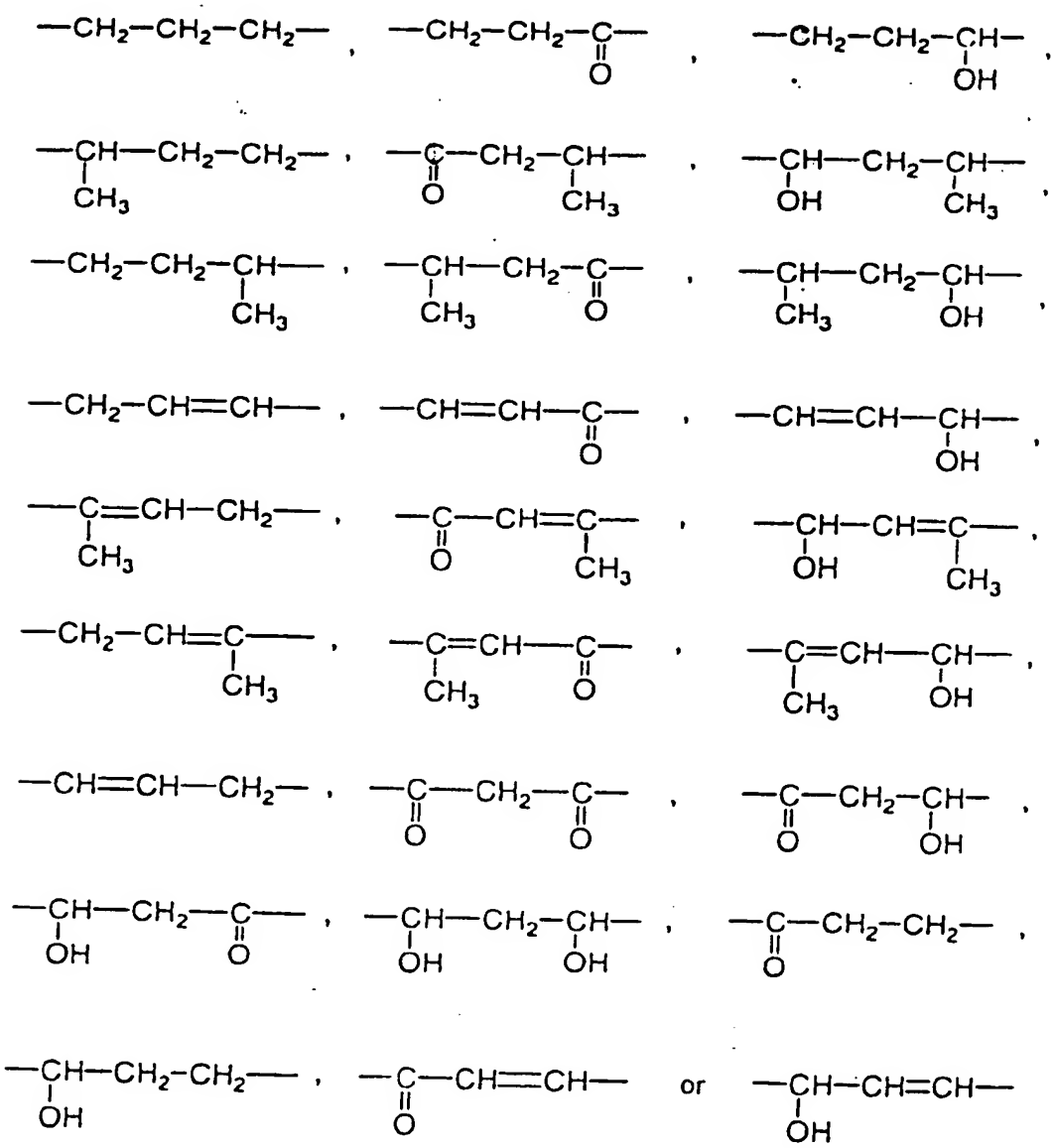


and -W-V- is



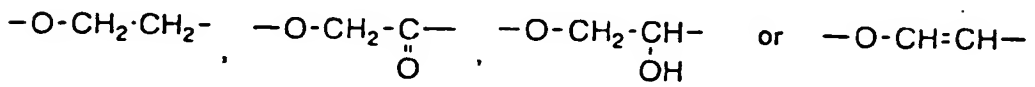
(13) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (10), wherein:

R^1 is -W-Z, wherein W is



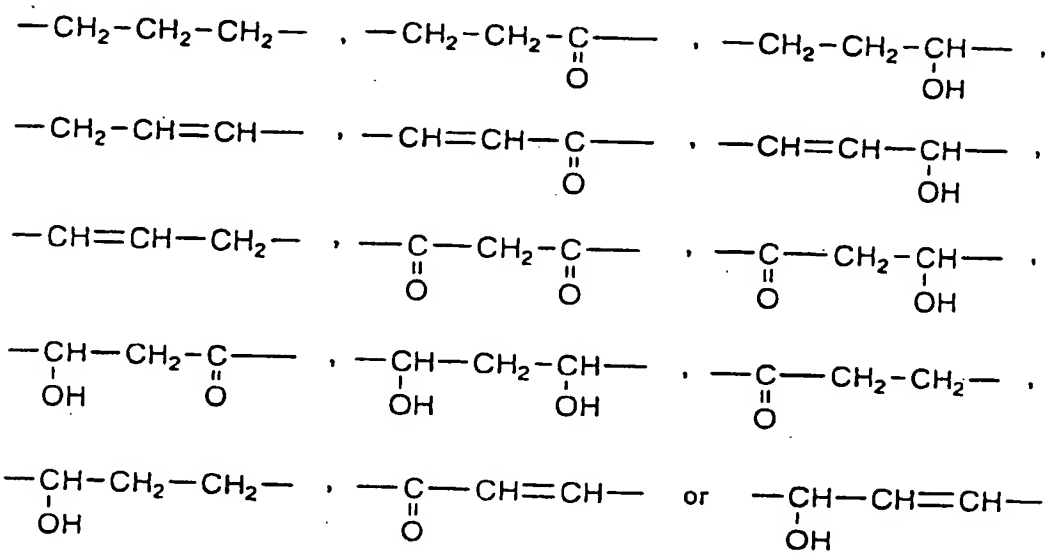
(14) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (11), wherein:

R^1 is -O-W-Z, wherein -O-W- is



(15) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (13), wherein:

R^1 is -W-Z, wherein W is



(16) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (5), (6) or (7), wherein:

Y is $-CH_2-$; and

R^4 is a hydrogen atom.

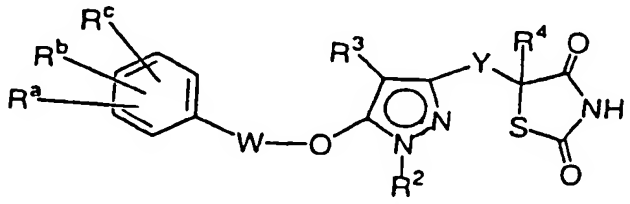
(17) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (5), (6) or (7),

wherein:

Y is CHR^7 (R^7 forms a bond together with R^4); and

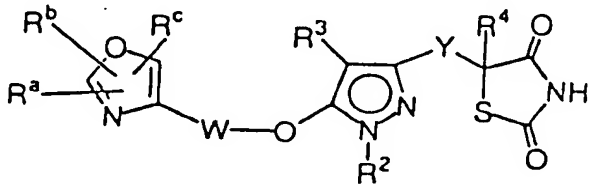
R^4 forms a bond together with R^7.

(18) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (14), which is represented by the formula:



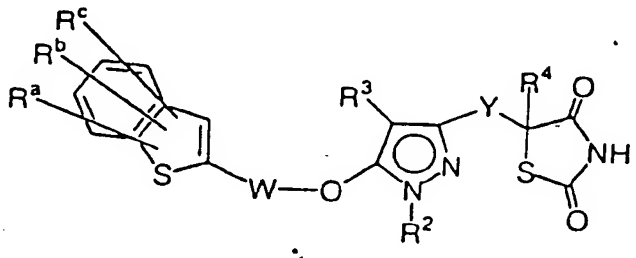
wherein each of R^a, R^b and R^c is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom or a phenyl group (said phenyl group may be substituted with at most 3 of a methyl group, a methoxy group and a chlorine atom), R^2 is a hydrogen atom, a C_1-C_7 alkyl group or a phenyl group, R^3 is a hydrogen atom or a C_1-C_7 alkyl group, Y is CR^6R^7 (R^6 is a hydrogen atom or a methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4), and R^4 is a hydrogen atom, or forms a bond together with R^7.

(19) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (14), which is represented by the formula:



wherein each of R^a, R^b and R^c is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom or a phenyl group (said phenyl group may be substituted with at most 3 of a methyl group, a methoxy group and a chlorine atom), R^2 is a hydrogen atom, a C_1-C_7 alkyl group or a phenyl group, R^3 is a hydrogen atom or a C_1-C_7 alkyl group, Y is CR^6R^7 (R^6 is a hydrogen atom or a methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4), and R^4 is a hydrogen atom, or forms a bond together with R^7.

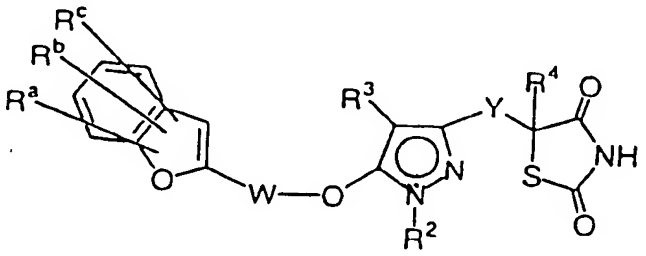
(20) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (14), which is represented by the formula:



wherein each of R^a, R^b and R^c is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom or a phenyl group (said phenyl group may be substituted with at most 3 of a methyl group, a methoxy group and a chlorine atom), R^2 is a hydrogen atom, a C_1-C_7 alkyl group or a phenyl group, R^3 is a hydrogen atom or a C_1-C_7 alkyl group, Y is CR^6R^7 (R^6 is a hydrogen atom or a

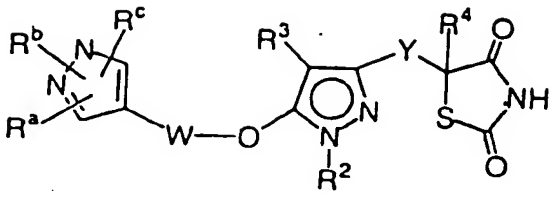
methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4), and R^4 is a hydrogen atom, or forms a bond together with R^7.

(21) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (14), which is represented by the formula:



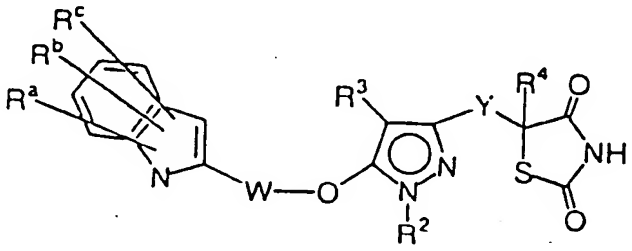
wherein each of R^a, R^b and R^c is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom or a phenyl group (said phenyl group may be substituted with at most 3 of a methyl group, a methoxy group and a chlorine atom), R^2 is a hydrogen atom, a C_1-C_7 alkyl group or a phenyl group, R^3 is a hydrogen atom or a C_1-C_7 alkyl group, Y is CR^6R^7 (R^6 is a hydrogen atom or a methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4), and R^4 is a hydrogen atom, or forms a bond together with R^7.

(22) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (14), which is represented by the formula:



wherein each of R^a, R^b and R^c is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom or a phenyl group (said phenyl group may be substituted with at most 3 of a methyl group, a methoxy group and a chlorine atom), R^2 is a hydrogen atom, a C_1-C_7 alkyl group or a phenyl group, R^3 is a hydrogen atom or a C_1-C_7 alkyl group, Y is CR^6R^7 (R^6 is a hydrogen atom or a methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4), and R^4 is a hydrogen atom, or forms a bond together with R^7.

(23) The pyrazole type thiazolidine compound and its salt according to the above-mentioned (14), which is represented by the formula:

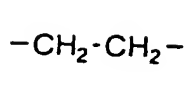


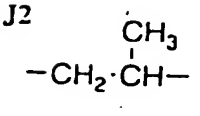
wherein each of R^a, R^b and R^c is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom or a phenyl group (said phenyl group may be substituted with

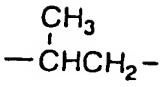
at most 3 of a methyl group, a methoxy group and a chlorine atom), R^2 is a hydrogen atom, a C_1-C_7 alkyl group or a phenyl group, R^3 is a hydrogen atom or a C_1-C_7 alkyl group, Y is CR^6R^7 (R^6 is a hydrogen atom or a methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4), and R^4 is a hydrogen atom, or forms a bond together with R^7.

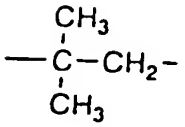
The following Tables 1 to 23 illustrate examples of the compounds of the present invention. Further, the salts derived by treating a basic nitrogen at the 3-position of the thiazolidine ring by means of a well known method are also the compounds of the present invention.

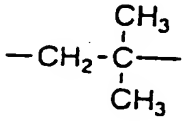
In the Tables, Q1 to Q90 and J1 to J54 represent the following substituents:

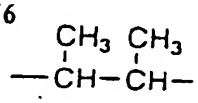
J1 

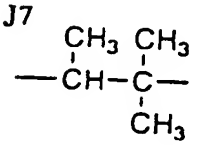
J2 

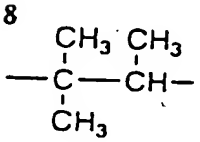
J3 

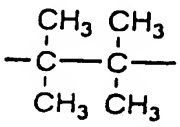
J4 

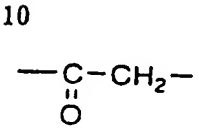
J5 

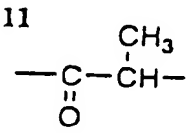
J6 

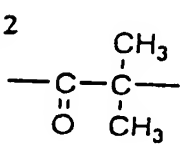
J7 

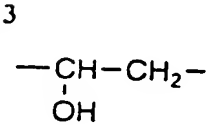
J8 

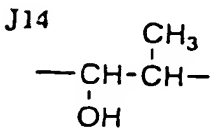
J9 

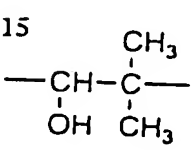
J10 

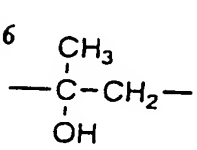
J11 

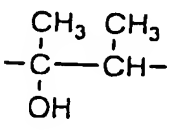
J12 

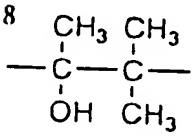
J13 

J14 

J15 

J16 

J17 

J18 

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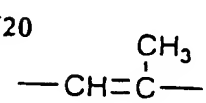
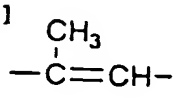
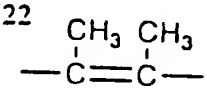
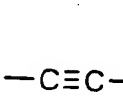
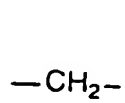
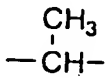
J20 

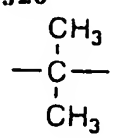
J21 

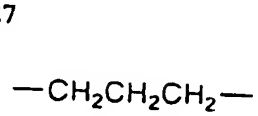
J22 

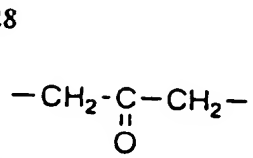
J23 

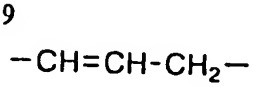
J24 

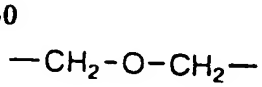
J25 

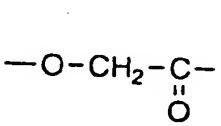
J26 

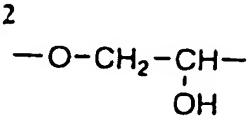
J27 

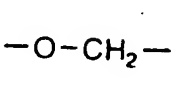
J28 

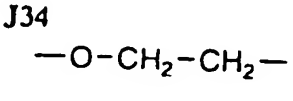
J29 

J30 

J31 

J32 

J33 

J34 

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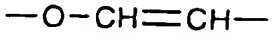

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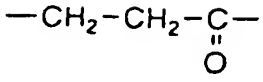

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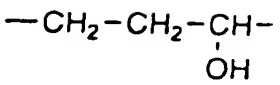

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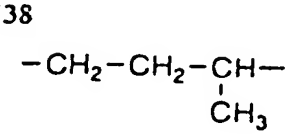

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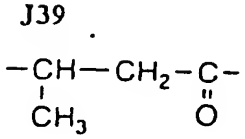

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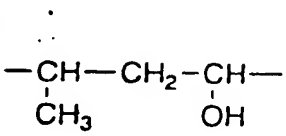

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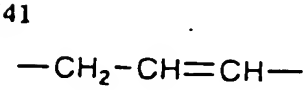

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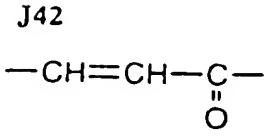

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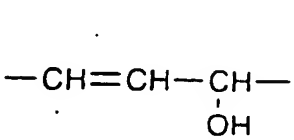

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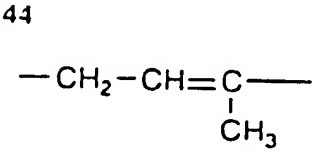

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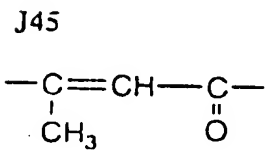

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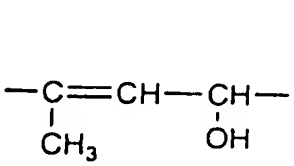

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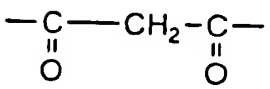

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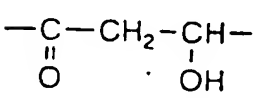

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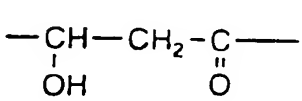

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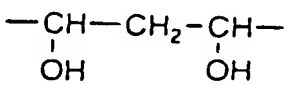

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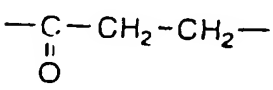

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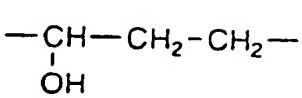

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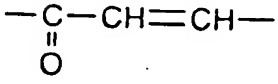

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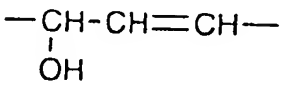
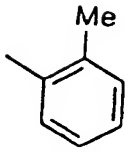
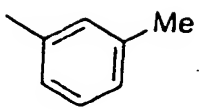
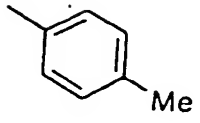
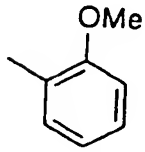
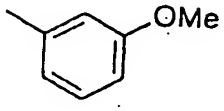


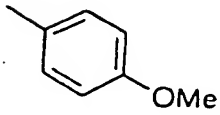
Q1 

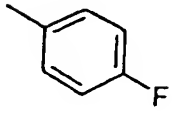
Q2 

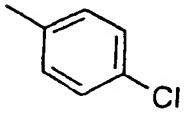
Q3 

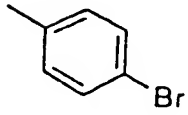
Q4 

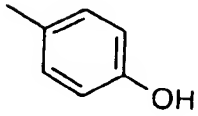
Q5 

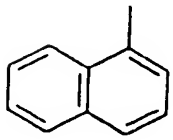
Q6 

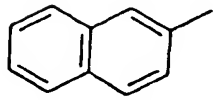
Q7 

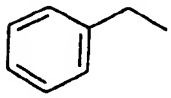
Q8 

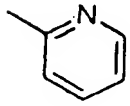
Q9 

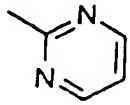
Q10 

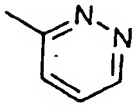
Q11 

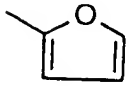
Q12 

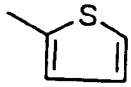
Q13 

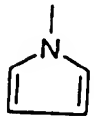
Q14 

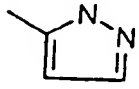
Q15 

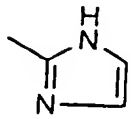
Q16 

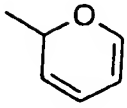
Q17 

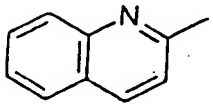
Q18 

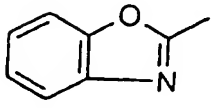
Q19 

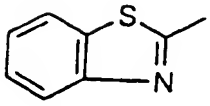
Q20 

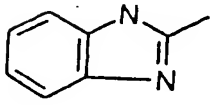
Q21 

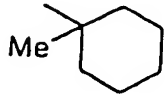
Q22 

Q23 

Q24 

Q25 

Q26 

Q 27 

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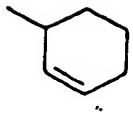

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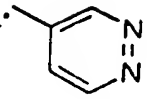

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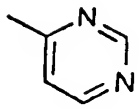

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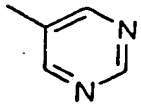

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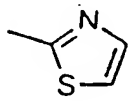

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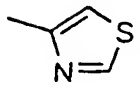

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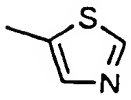

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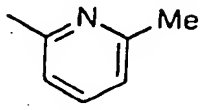

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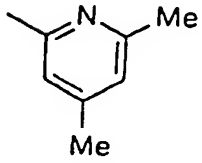

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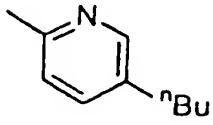

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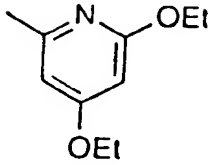

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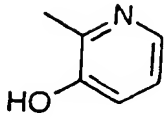

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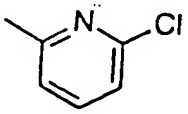

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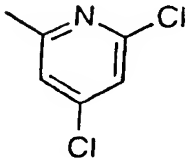

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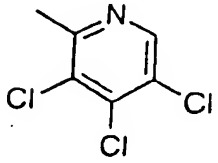

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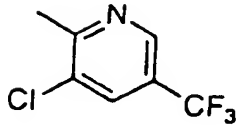

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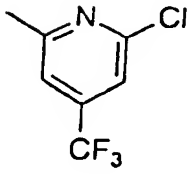

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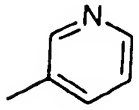

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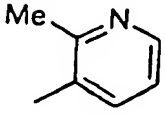

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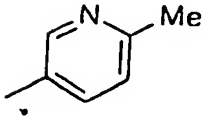

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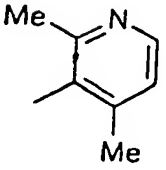

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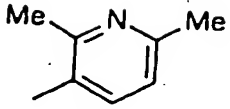

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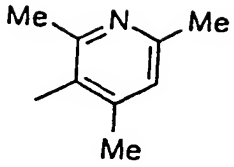

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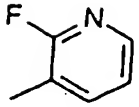

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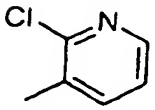

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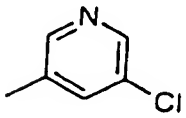

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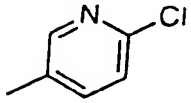

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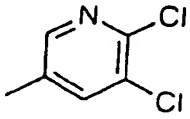

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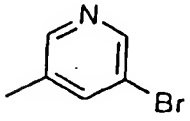

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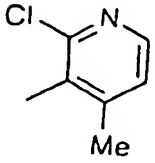

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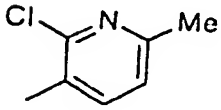

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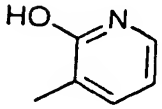

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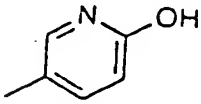

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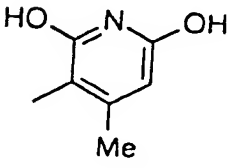

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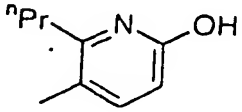

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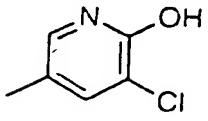

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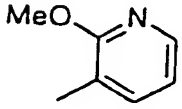

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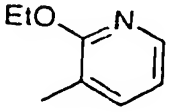

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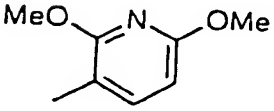

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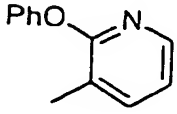

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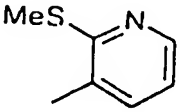

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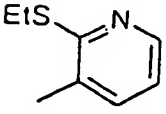

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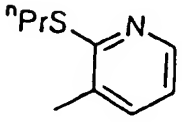

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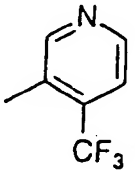

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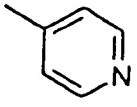
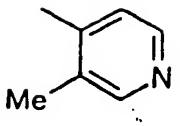
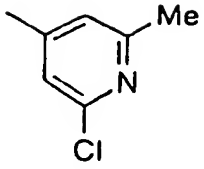
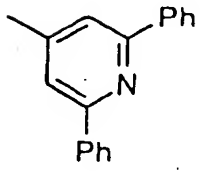
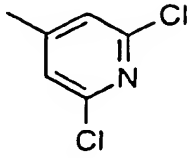
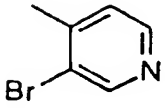


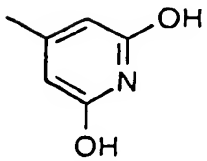
Q73 

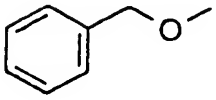
Q74 

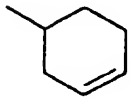
Q75 

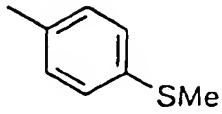
Q76 

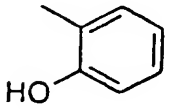
Q77 

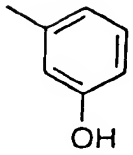
Q78 

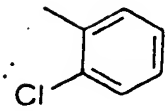
Q79 

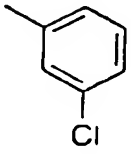
Q80 

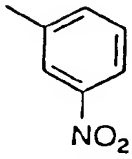
Q81 

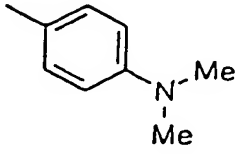
Q82 

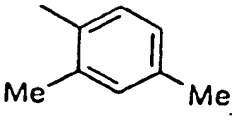
Q83 

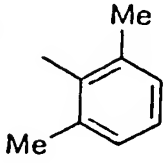
Q84 

Q85 

Q86 

Q87 

Q88 

Q89 

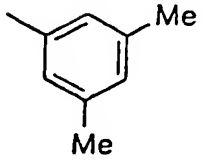
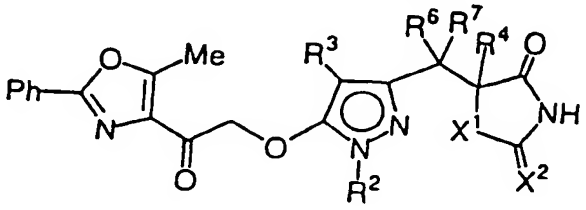
Q90 

Table 1

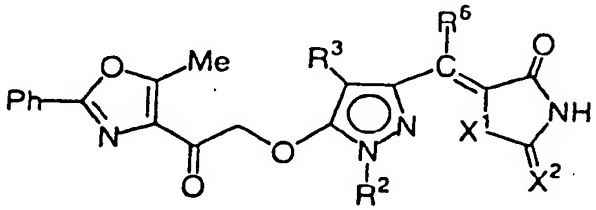


wherein X^1, X^2, R^2, R^3, R^4, R^6 and R^7 are as identified in the following Table.

X^1	X^2	R^2	R^3	R^4	R^6	R^7
S	O	Me	H	H	H	H
S	S	Me	H	H	H	H
O	S	Me	H	H	H	H
O	O	Me	H	H	H	H
S	NH	Me	H	H	H	H
O	NH	Me	H	H	H	H
S	O	^{t}Bu	H	H	H	H
S	S	^{t}Bu	H	H	H	H
O	S	^{t}Bu	H	H	H	H
O	O	^{t}Bu	H	H	H	H
S	NH	^{t}Bu	H	H	H	H
O	NH	^{t}Bu	H	H	H	H
S	O	Ph	H	H	H	H
S	S	Ph	H	H	H	H
O	S	Ph	H	H	H	H
O	O	Ph	H	H	H	H
S	NH	Ph	H	H	H	H
O	NH	Ph	H	H	H	H
S	O	Me	H	H	H	H
S	S	Me	H	H	H	Me
O	S	Me	H	H	H	Me
O	O	Me	H	H	H	Me
S	NH	Me	H	H	H	Me
O	NH	Me	H	H	H	Me
S	O	^{t}Bu	H	H	H	Me
S	S	^{t}Bu	H	H	H	Me
O	S	^{t}Bu	H	H	H	Me
O	O	^{t}Bu	H	H	H	Me
S	NH	^{t}Bu	H	H	H	Me
O	NH	^{t}Bu	H	H	H	Me
S	O	Ph	H	H	H	Me
S	S	Ph	H	H	H	Me
O	S	Ph	H	H	H	Me
O	O	Ph	H	H	H	Me

S	NH	Ph	H	H	H	Me
O	NH	Ph	H	H	H	Me
S	O	Me	H	Me	H	H
S	S	Me	H	Me	H	H
O	S	Me	H	Me	H	H
O	O	Me	H	Me	H	H
S	NH	Me	H	Me	H	H
O	NH	Me	H	Me	H	H
S	O	^{t}Bu	H	Me	H	H
S	S	^{t}Bu	H	Me	H	H
O	S	^{t}Bu	H	Me	H	H
O	O	^{t}Bu	H	Me	H	H
S	NH	^{t}Bu	H	Me	H	H
O	NH	^{t}Bu	H	Me	H	H
S	O	Ph	H	Me	H	H
S	S	Ph	H	Me	H	H
O	S	Ph	H	Me	H	H
O	O	Ph	H	Me	H	H
S	NH	Ph	H	Me	H	H
O	NH	Ph	H	Me	H	H
S	O	Me	H	Me	H	Me
S	S	Me	H	Me	H	Me
O	S	Me	H	Me	H	Me
O	O	Me	H	Me	H	Me
S	NH	Me	H	Me	H	Me
O	NH	Me	H	Me	H	Me
S	O	^{t}Bu	H	Me	H	Me
S	S	^{t}Bu	H	Me	H	Me
O	S	^{t}Bu	H	Me	H	Me
O	O	^{t}Bu	H	Me	H	Me
S	NH	^{t}Bu	H	Me	H	Me
O	NH	^{t}Bu	H	Me	H	Me
S	O	Ph	H	Me	H	Me
S	S	Ph	H	Me	H	Me
O	S	Ph	H	Me	H	Me
O	O	Ph	H	Me	H	Me
S	NH	Ph	H	Me	H	Me
O	NH	Ph	H	Me	H	Me

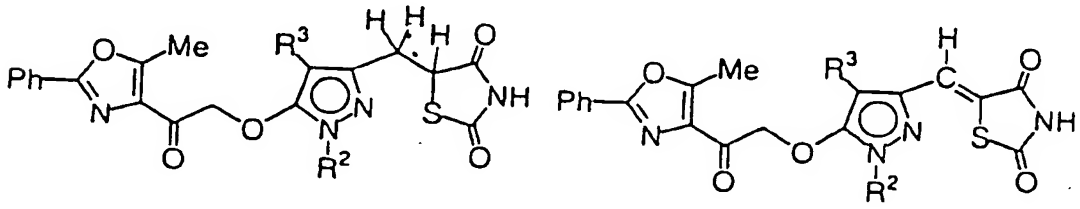
Table 2



wherein X^1, X^2, R^2, R^3 and R^6 are as identified in the following Table.

X^1	X^2	R^2	R^3	R^6	X^1	X^2	R^2	R^3	R^6
S	O	Me	H	H	S	O	Me	H	Me
S	S	Me	H	H	S	S	Me	H	Me
O	S	Me	H	H	O	S	Me	H	Me
O	O	Me	H	H	O	O	Me	H	Me
S	NH	Me	H	H	S	NH	Me	H	Me
O	NH	Me	H	H	O	NH	Me	H	Me
S	O	^{t}Bu	H	H	S	O	^{t}Bu	H	Me
S	S	^{t}Bu	H	H	S	S	^{t}Bu	H	Me
O	S	^{t}Bu	H	H	O	S	^{t}Bu	H	Me
O	O	^{t}Bu	H	H	O	O	^{t}Bu	H	Me
S	NH	^{t}Bu	H	H	S	NH	^{t}Bu	H	Me
O	NH	^{t}Bu	H	H	O	NH	^{t}Bu	H	Me
S	O	Ph	H	H	S	O	Ph	H	Me
S	S	Ph	H	H	S	S	Ph	H	Me
O	S	Ph	H	H	O	S	Ph	H	Me
O	O	Ph	H	H	O	O	Ph	H	Me
S	NH	Ph	H	H	S	NH	Ph	H	Me
O	NH	Ph	H	H	O	NH	Ph	H	Me

Table 3



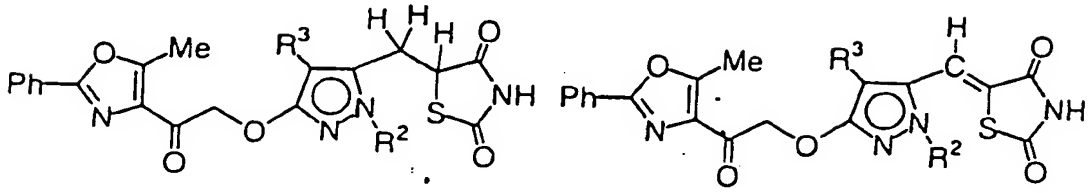
wherein R^2 and R^3 are as identified in the following Table.

R^2	R^3	R^2	R^3	R^2	R^3	R^2	R^3
H	H	^{i}Pr	Cl	^{t}Bu	Ph	^{c}Pr	Et
H	Me	^{i}Pr	Br	^{t}Bu	Cl	^{c}Pr	Ph
Me	Me	^{n}Bu	H	^{t}Bu	Br	^{c}Pr	Cl
Me	Et	^{n}Bu	Me	^{n}Pen	H	^{c}Pr	Br
Me	Ph	^{n}Bu	Et	^{n}Pen	Me	^{c}Bu	H
Me	Cl	^{n}Bu	Ph	^{n}Pen	Et	^{c}Bu	Me
Me	Br	^{n}Bu	Cl	^{n}Pen	Ph	^{c}Bu	Et
Et	H	^{n}Bu	Br	^{n}Pen	Cl	^{c}Bu	Ph

Et	Me	^{i}Bu	H	^{n}Pen	Br	^{c}Bu	Cl
Et	Et	^{i}Bu	Me	^{n}Hex	H	^{c}Bu	Br
Et	Ph	^{i}Bu	Et	^{n}Hex	Me	^{c}Pen	H
Et	Cl	^{i}Bu	Ph	^{n}Hex	Et	^{c}Pen	Me
Et	Br	^{i}Bu	Cl	^{n}Hex	Ph	^{c}Pen	Et
^{n}Pr	H	^{i}Bu	Br	^{n}Hex	Cl	^{c}Pen	Ph
^{n}Pr	Me	^{s}Bu	H	^{n}Hex	Br	^{c}Pen	Cl
^{n}Pr	Et	^{s}Bu	Me	^{n}Hep	H	^{c}Pen	Br
^{n}Pr	Ph	^{s}Bu	Et	^{n}Hep	Me	^{c}Hex	H
^{n}Pr	Cl	^{s}Bu	Ph	^{n}Hep	Et	^{c}Hex	Me
^{n}Pr	Br	^{s}Bu	Cl	^{n}Hep	Ph	^{c}Hex	Et
^{i}Pr	H	^{s}Bu	Br	^{n}Hep	Cl	^{c}Hex	Ph
^{i}Pr	Me	^{t}Bu	H	^{n}Hep	Br	^{c}Hex	Cl
^{i}Pr	Et	^{t}Bu	Me	^{c}Pr	H	^{c}Hex	Br
^{i}Pr	Ph	^{t}Bu	Et	^{c}Pr	Me	Q1	H
Q1	Me	Q5	H	Q8	Br	Q12	Cl
Q1	Et	Q5	Me	Q9	H	Q12	Br
Q1	Ph	Q5	Et	Q9	Me	Q13	H
Q1	Cl	Q5	Ph	Q9	Et	Q13	Me
Q1	Br	Q5	Cl	Q9	Ph	Q13	Et
Q2	H	Q5	Br	Q9	Cl	Q13	Ph
Q2	Me	Q6	H	Q9	Br	Q13	Cl
Q2	Et	Q6	Me	Q10	H	Q13	Br
Q2	Ph	Q6	Et	Q10	Me	Q14	H
Q2	Cl	Q6	Ph	Q10	Et	Q14	Me
Q2	Br	Q6	Cl	Q10	Ph	Q14	Et
Q3	H	Q6	Br	Q10	Cl	Q14	Ph
Q3	Me	Q7	H	Q10	Br	Q14	Cl
Q3	Et	Q7	Me	Q11	H	Q14	Br
Q3	Ph	Q7	Et	Q11	Me	Q15	H
Q3	Cl	Q7	Ph	Q11	Et	Q15	Me
Q3	Br	Q7	Cl	Q11	Ph	Q15	Et
Q4	H	Q7	Br	Q11	Cl	Q15	Ph
Q4	Me	Q8	H	Q11	Br	Q15	Cl
Q4	Et	Q8	Me	Q12	H	Q15	Br
Q4	Ph	Q8	Et	Q12	Me	Q16	H
Q4	Cl	Q8	Ph	Q12	Et	Q16	Me
Q4	Br	Q8	Cl	Q12	Ph	Q16	Et
Q16	Ph	Q20	Me	Q23	Br		
Q16	Cl	Q20	Et	Q24	H		
Q16	Br	Q20	Ph	Q24	Me		
Q17	H	Q20	Cl	Q24	Et		
Q17	Me	Q20	Br	Q24	Ph		
Q17	Et	Q21	H	Q24	Cl		
Q17	Ph	Q21	Me	Q24	Br		
Q17	Cl	Q21	Et	Q25	H		
Q17	Br	Q21	Ph	Q25	Me		
Q18	H	Q21	Cl	Q25	Et		
Q18	Me	Q21	Br	Q25	Ph		
Q18	Et	Q22	H	Q25	Cl		
Q18	Ph	Q22	Me	Q25	Br		
Q18	Cl	Q22	Et	Q26	H		
Q18	Br	Q22	Ph	Q26	Me		
Q19	H	Q22	Cl	Q26	Et		

Q19	Me	Q22	Br	Q26	Ph
Q19	Et	Q23	H	Q26	Cl
Q19	Ph	Q23	Me	Q26	Br
Q19	Cl	Q23	Et		
Q19	Br	Q23	Ph		
Q20	H	Q23	Cl		

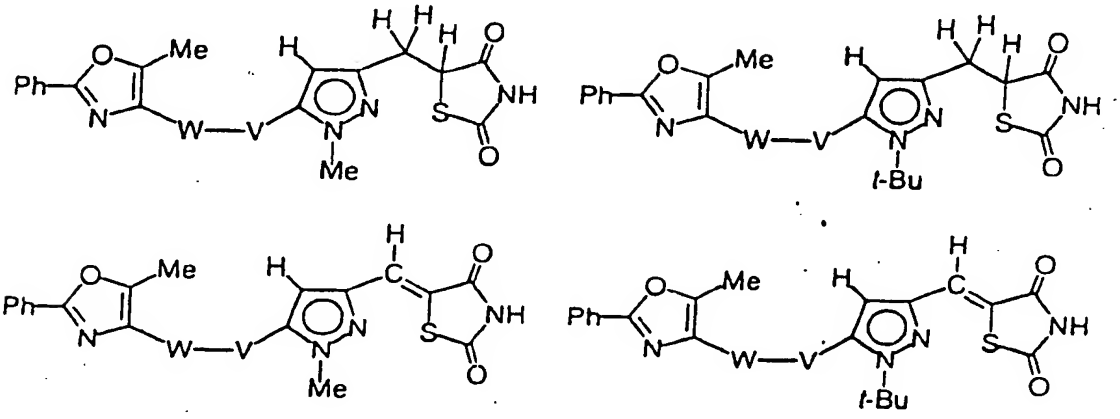
Table 4



wherein R^2 and R^3 are as identified in the following Table.

R^2	R^3
Me	H
Et	H
Ph	H
Me	Me
Me	Cl
Me	Br
^{i}Pr	Me
^{i}Pr	Cl
^{i}Pr	Br
^{t}Bu	Me
^{t}Bu	Cl
^{t}Bu	Br

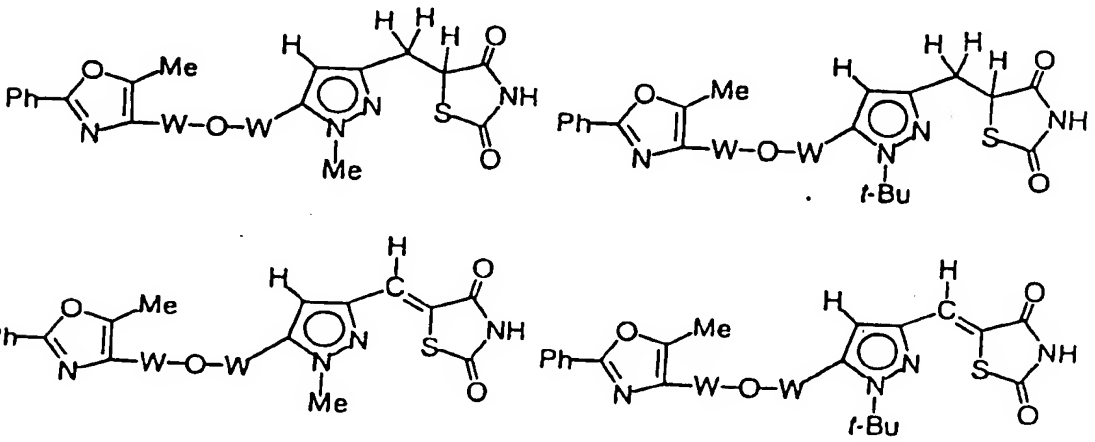
Table 5



wherein W and V are as identified in the following Table.

W	V	W	V	W	V	W	V
J1	O	J11	O	J20	O	J29	O
J2	O	J12	O	J21	O	J10	S
J3	O	J13	O	J22	O	J10	SO
J4	O	J14	O	J23	O	J10	SO_2
J5	O	J15	O	J24	O	J10	NH
J6	O	J16	O	J25	O	J10	NMe
J7	O	J17	O	J26	O		
J8	O	J18	O	J27	O		
J9	O	J19	O	J28	O		

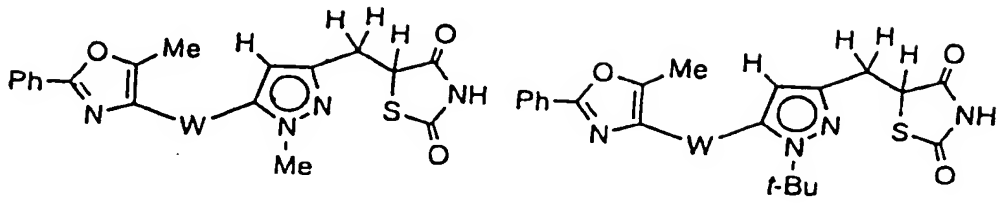
Table 6



wherein W-O-W is as identified in the following Table.

W-O-W
J30
J31
J32
J33
J34
J35

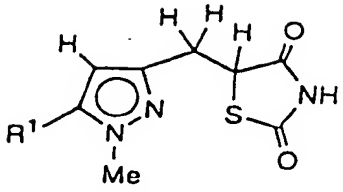
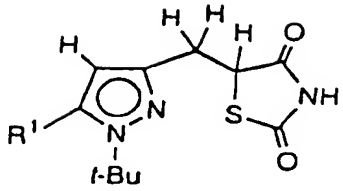
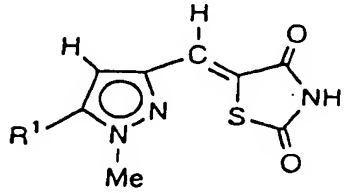
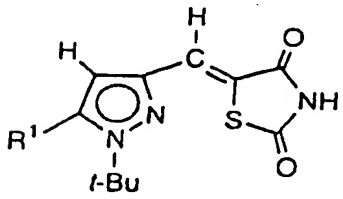
Table 7



wherein W is as identified in the following Table.

W	W	W	W
J27	J40	J45	J50
J29	J41	J46	J51
J36	J42	J47	J52
J37	J43	J48	J53
J38	J44	J49	J54
J39			

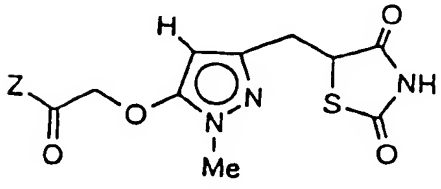
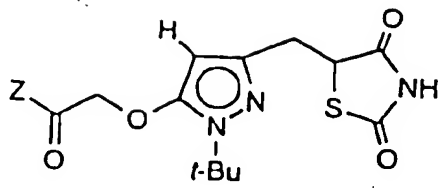
Table 8

wherein R^1 is as identified in the following Table.

R^1
n-Hexyl
1-Hexenyl
1-Hexynyl
n-Hexyloxy
2-Hexenyloxy
n-Hexylthio
n-Hexylamino
N-Methyl-N-n-hexylamino

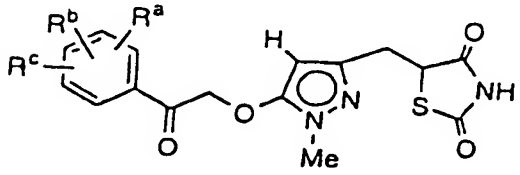
Table 9

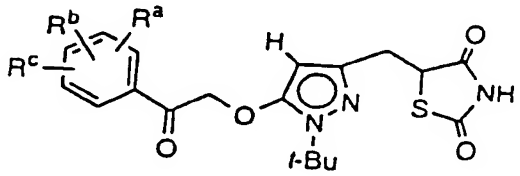



wherein Z is as identified in the following Table.

Z	Z	Z	Z	Z	Z
^{c}Hex	Q31	Q41	Q51	Q61	Q71
Q27	Q32	Q42	Q52	Q62	Q72
Q28	Q33	Q43	Q53	Q63	Q73
Q11	Q34	Q44	Q54	Q64	Q74
Q12	Q35	Q45	Q55	Q65	Q75
Q14	Q36	Q46	Q56	Q66	Q76
Q15	Q37	Q47	Q57	Q67	Q77
Q16	Q38	Q48	Q58	Q68	Q78
Q29	Q39	Q49	Q59	Q69	
Q30	Q40	Q50	Q60	Q70	

Table 10

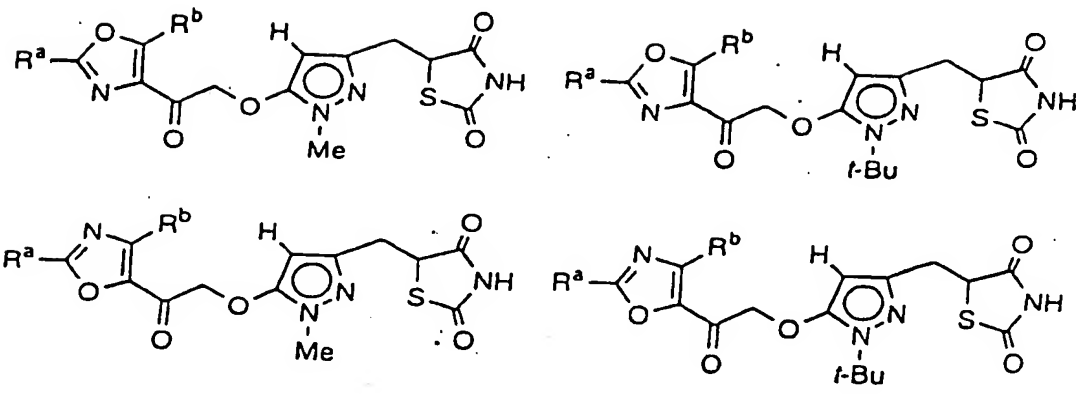




wherein R^a, R^b and R^c are as identified in the following Table.

R^a	R^b	R^c	R^a	R^b	R^c
2-Me	H	H	4-Q79	H	H
3-Me	H	H	2-OH	H	H
4-Me	H	H	3-OH	H	H
2-OMe	H	H	4-OH	H	H
3-OMe	H	H	2-F	H	H
4-OMe	H	H	3-F	H	H
2-Ph	H	H	4-F	H	H
3-Ph	H	H	2-Cl	H	H
4-Ph	H	H	3-Cl	H	H
4-Q11	H	H	4-Cl	H	H
4-Q17	H	H	2-Br	H	H
4-Q18	H	H	3-Br	H	H
4-Q45	H	H	4-Br	H	H
4-Q13	H	H	3-CF_3	H	H
4-OPh	H	H			

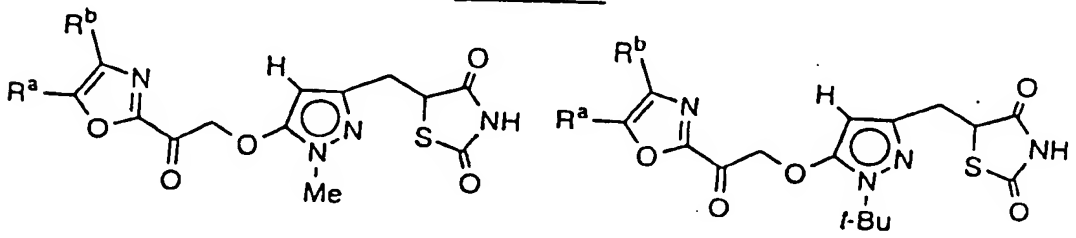
Table 11



wherein R^a and R^b are as identified in the following Table.

R^a	R^b	R^a	R^b	R^a	R^b
H	Me	Q81	Me	Q18	Me
Me	Me	Q82	Me	Q14	Me
Et	Me	Q83	Me	Q45	Me
^{n}Pr	Me	Q10	Me	Q72	Me
^{i}Pr	Me	Q7	Me	Q13	Me
^{t}Bu	Me	Q84	Me	OPh	Me
^{c}Pr	Me	Q85	Me	Q79	Me
^{c}Hex	Me	Q8	Me	Ph	H
Q80	Me	Q9	Me	Ph	Me
Ph	Me	Q86	Me	Ph	Et
Q1	Me	Q87	Me	Ph	^{n}Pr
Q2	Me	Q88	Me	Ph	^{i}Pr
Q3	Me	4-Ph-Ph	Me	Ph	^{t}Bu
Q4	Me	Q11	Me	Ph	^{c}Pr
Q5	Me	Q12	Me	Ph	^{c}Hex
Q6	Me	Q17	Me	Ph	Ph

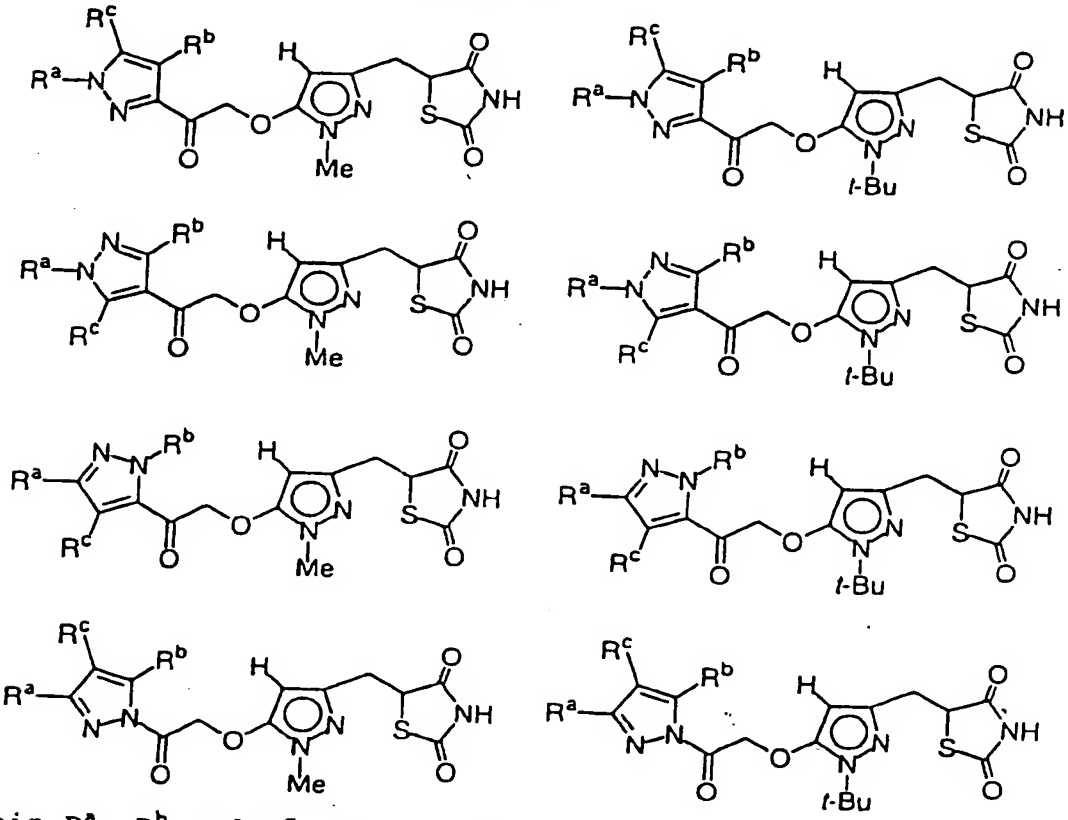
Table 12



wherein R^a and R^b are as identified in the following Table.

R^a	R^b	R^a	R^b
H	H	^{c}Hex	H
H	Me	^{c}Hex	Me
H	^{c}Hex	^{c}Hex	^{c}Hex
H	Ph	^{c}Hex	Ph
Me	H	Ph	H
Me	Me	Ph	Me
Me	^{c}Hex	Ph	^{c}Hex
Me	Ph	Ph	Ph

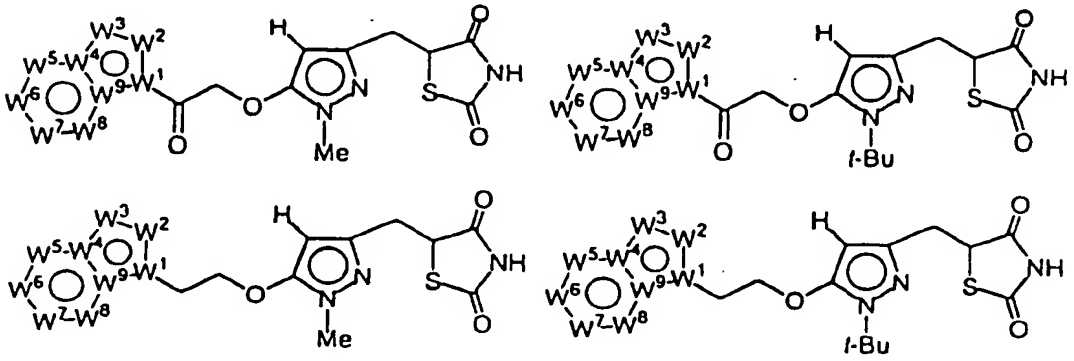
Table 13



wherein R^a, R^b and R^c are as identified in the following Table.

R^a	R^b	R^c	R^a	R^b	R^c
H	Me	H	Q86	Me	H
Me	Me	H	Q87	Me	H
Et	Me	H	Q88	Me	H
^{n}Pr	Me	H	4-Ph-Ph	Me	H
^{i}Pr	Me	H	Q11	Me	H
^{t}Bu	Me	H	Q12	Me	H
^{c}Pr	Me	H	Q17	Me	H
^{c}Hex	Me	H	Q18	Me	H
Q80	Me	H	Q14	Me	H
Ph	Me	H	Q45	Me	H
Q1	Me	H	Q72	Me	H
Q2	Me	H	Q13	Me	H
Q3	Me	H	OPh	Me	H
Q4	Me	H	Q79	Me	H
Q5	Me	H	Ph	H	H
Q6	Me	H	Ph	Me	H
Q81	Me	H	Ph	Et	H
Q82	Me	H	Ph	^{n}Pr	H
Q83	Me	H	Ph	^{i}Pr	H
Q10	Me	H	Ph	^{t}Bu	H
Q7	Me	H	Ph	^{c}Pr	H
Q84	Me	H	Ph	^{c}Hex	H
Q85	Me	H	Ph	Ph	H
Q8	Me	H	Ph	Me	Me
Q9	Me	H			

Table 14

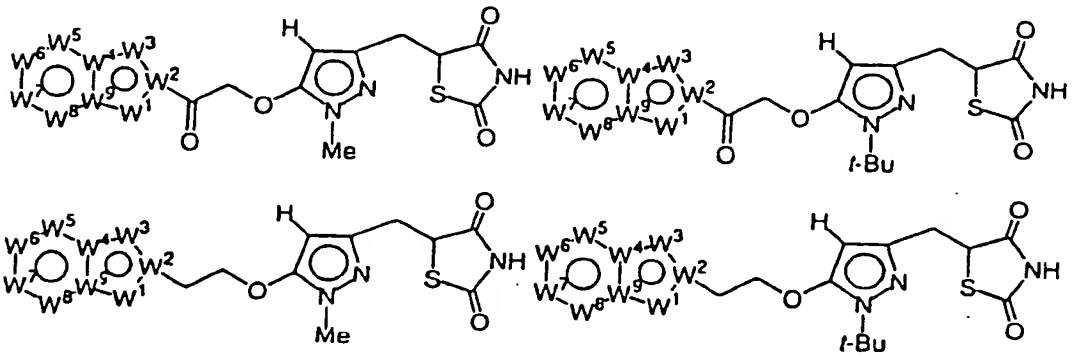


wherein W^1, W^2, W^3, W^4, W^5, W^6, W^7, W^8 and W^9 are as identified in the following Table.

W^1	W^2	W^3	W^4	W^5	W^6	W^7	W^8	W^9
CH	CH	CH	C	CH	CH	CH	CH	C
C	CMe	NH	C	CH	CH	CH	CH	C
C	CMe	NMe	C	CH	CH	CH	CH	C
C	CH	NH	C	CH	CH	CH	CH	C
C	CH	S	C	CH	CH	CH	CH	C
N	CH	N	C	CH	CH	CH	CH	C
C	CH	O	C	CH	CH	CH	CH	C
C	CH	CH	C	CH	CH	CH	CH	C
C	N	NH	C	CH	CH	CH	CH	N
C	N	NMe	C	CH	CH	CH	CH	C
N	N	N	C	CH	CH	CH	CH	C
N	CH	N	C	N	CH	N	CH	C
C	CH	N	N	CH	CH	CH	N	C
C	CH	N	N	CH	CH	N	N	C
C	CMe	S	C	N	CCF_3	N	-*	N
C	CMe	S	C	N	CMe	N	-	N
C	CH	S	C	N	CH	N	-	N

* : covalent bond

Table 15



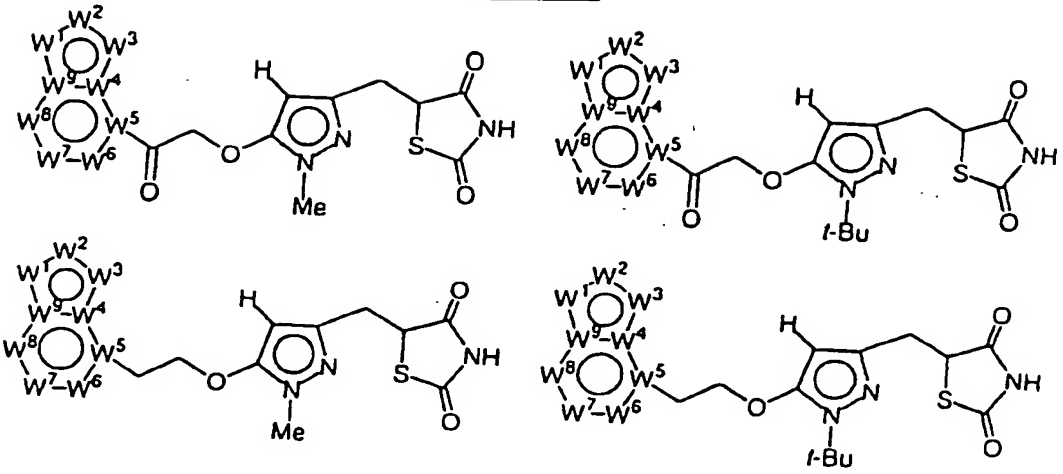
wherein W^1, W^2, W^3, W^4, W^5, W^6, W^7, W^8 and W^9 are as identified in the following Table.

W^1	W^2	W^3	W^4	W^5	W^6	W^7	W^8	W^9
CH_2	C	CMe	C	CH	CH	CH	CH	C

CH_2	C	CH	C	CH	CH	CH	CH	C
NMe	C	CH	C	CH	CH	CH	CH	C
NH	C	CH	C	CH	CH	CH	CH	C
NMe	C	CMe	C	CH	CH	CH	CH	C
NH	C	CMe	C	CH	CH	CH	CH	C
NH	C	CH	C	CH	CMe	CH	CH	C
NH	C	CH	C	CH	CBr	CH	CH	C
NH	C	CH	C	CH	CPh	CH	CH	C
NMe	C	CH	C	CH	CMe	CH	CH	C
NMe	C	CH	C	CH	CBr	CH	CH	C
NMe	C	CH	C	CH	CPh	CH	CH	C
S	C	CMe	C	CH	CCl	CH	CH	C
S	C	CMe	C	CH	CH	CH	CH	C
S	C	CH	C	CH	CH	CH	CH	C
S	C	CH	C	CH	CPh	CH	CH	C
S	C	CMe	C	CH	CPh	CH	CH	C
O	C	CH	C	CH	CH	CH	COMe	C
O	C	CMe	C	CH	CH	CH	CH	C
O	C	CH	C	CH	CH	CH	CH	C
O	C	CH	C	CH	CPh	CH	CH	C
O	C	CMe	C	CH	CPh	CH	CH	C
NH	C	N	C	CH	CH	CH	CH	C
NMe	C	N	C	CH	CH	CH	CH	C
NH	C	N	C	CH	CMe	CMe	CH	C
NMe	C	N	C	CH	CMe	CMe	CH	C
NH	C	N	C	CH	CPh	CH	CH	C
NMe	C	N	C	CH	CPh	CH	CH	C
NMe	C	N	C	CH	CH	CPh	CH	C
N	C	O	C	CH	CH	CH	CH	C
N	C	O	C	CH	CPh	CH	CH	C
N	C	O	C	CH	CH	CPh	CH	C
N	C	O	C	CH	CMe	CH	CH	C
N	C	O	C	CH	CH	CMe	CH	C
N	C	S	C	CH	CH	CH	CH	C
N	C	S	C	CH	CPh	CH	CH	C
N	C	S	C	CH	CH	CPh	CH	C
N	C	S	C	CH	CMe	CH	CH	C
N	C	S	C	CH	CH	CMe	CH	C
CH	C	CH	C	CH	CH	CH	CH	N
NH	C	N	C	N	CH	N	CH	C
NMe	C	N	C	N	CH	N	CH	C
N	C	CH	C	N	CH	CH	CH	N
N	C	CH	C	N	N	CH	CH	N
S	C	CMe	N	N	CCF_3	N	-*	C
S	C	CMe	N	N	CMe	N	-	C
S	C	CH	N	N	CH	N	-	C

*: covalent bond

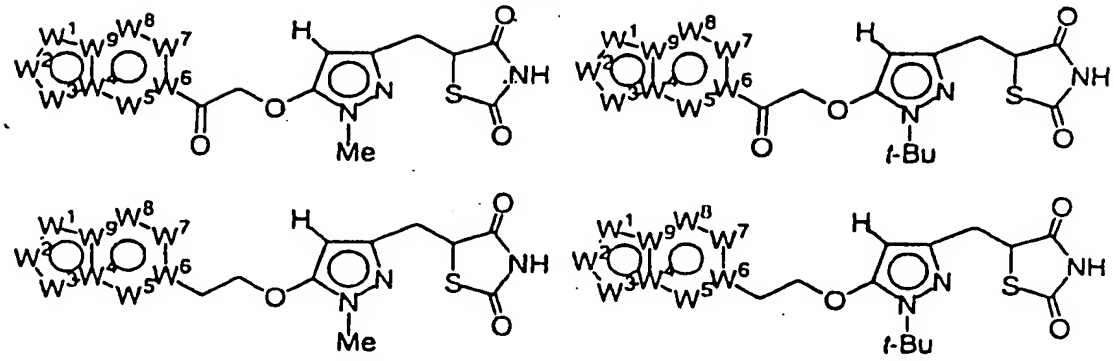
Table 16



wherein W^1, W^2, W^3, W^4, W^5, W^6, W^7, W^8 and W^9 are as identified in the following Table.

W^1	W^2	W^3	W^4	W^5	W^6	W^7	W^8	W^9
CH_2	CH	CH	C	C	CH	CH	CH	C
CH	CH	CH_2	C	C	CH	CH	CH	C
NMe	CH	CH	C	C	CH	CH	CH	C
CH	CH	NMe	C	C	CH	CH	CH	C
S	CH	CH	C	C	CH	CH	CH	C
CH	CH	S	C	C	CH	CH	CH	C
O	CH	CH	C	C	CH	CH	CH	C
CH	CH	O	C	C	CH	CH	CH	C
O	CH_2	CH_2	C	C	CH	CH	CH	C
CH_2	CH_2	O	C	C	CH	CH	CH	C
O	CH_2	O	C	C	CH	CH	CH	C
NH	C	N	C	C	CH	CH	CH	C
NMe	C	N	C	C	CH	CH	CH	C
N	C	NMe	C	C	CH	CH	CH	C
N	C	O	C	C	CH	CH	CH	C
O	C	N	C	C	CH	CH	CH	C
N	C	S	C	C	CH	CH	CH	C
S	C	N	C	C	CH	CH	CH	C
CH	CH	CH	C	C	CH	CH	CH	N
CH	CH	CH	N	C	CH	CH	CH	C
NH	CH	N	C	C	N	CH	N	C
CH	CH	N	N	C	CH	CH	N	C
CH	CH	N	N	C	CH	N	N	C

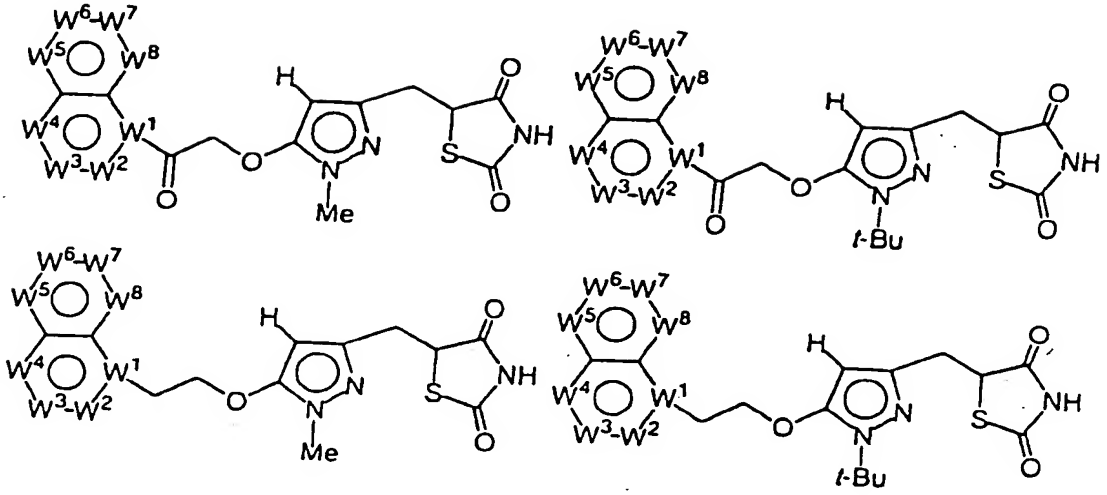
Table 17



wherein W^1, W^2, W^3, W^4, W^5, W^6, W^7, W^8 and W^9 are as identified in the following Table.

W^1	W^2	W^3	W^4	W^5	W^6	W^7	W^8	W^9
CH_2	CH	CH	C	CH	C	CH	CH	C
CH	CH	CH_2	C	CH	C	CH	CH	C
NMe	CH	CH	C	CH	C	CH	CH	C
CH	CH	NMe	C	CH	C	CH	CH	C
S	CH	CH	C	CH	C	CH	CH	C
CH	CH	S	C	CH	C	CH	CH	C
S	CH_2	CH_2	C	CH	C	CH	CH	C
CH_2	CH_2	S	C	CH	C	CH	CH	C
O	CH	CH	C	CH	C	CH	CH	C
CH	CH	O	C	CH	C	CH	CH	C
O	CH_2	CH_2	C	CH	C	CH	CH	C
CH_2	CH_2	O	C	CH	C	CH	CH	C
O	CH_2	O	C	CH	C	CH	CH	C
NH	C	N	C	CH	C	CH	CH	C
NMe	C	N	C	CH	C	CH	CH	C
N	C	NMe	C	CH	C	CH	CH	C
N	C	O	C	CH	C	CH	CH	C
O	C	N	C	CH	C	CH	CH	C
N	C	S	C	CH	C	CH	CH	C
S	C	N	C	CH	C	CH	CH	C
CH	CH	CH	C	CH	C	CH	CH	N
CH	CH	CH	N	CH	C	CH	CH	C
NH	CH	N	C	N	C	N	CH	C
CH	CH	N	N	CH	C	CH	N	C
CH	CMe	N	N	CMe	C	CH	N	C
CH	CH	N	N	CH	C	N	N	C
CH	CMe	N	N	CMe	C	N	N	C
CH	CPh	N	N	CMe	C	CH	N	C
CH	CPh	N	N	CMe	C	N	N	C

Table 18

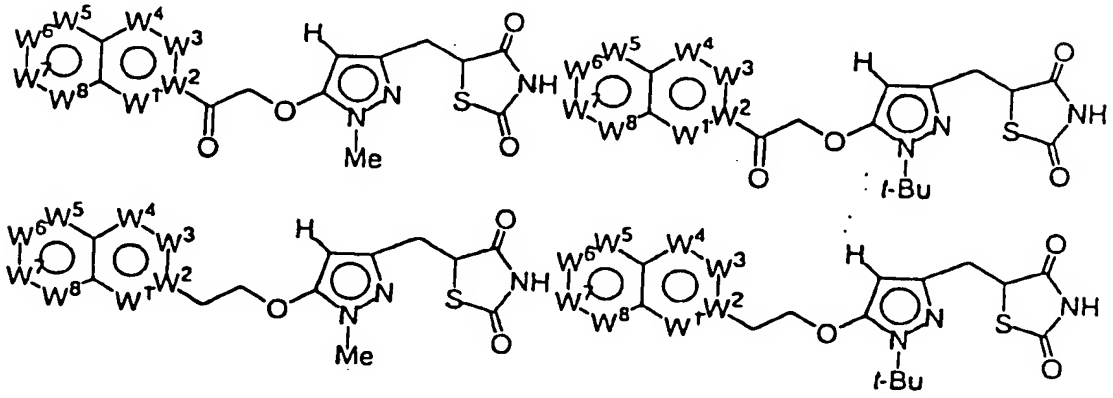


wherein W^1, W^2, W^3, W^4, W^5, W^6, W^7 and W^8 are as identified in the following Table.

W^1	W^2	W^3	W^4	W^5	W^6	W^7	W^8
C	CH	CH	CH	CH	CH	CH	CH
C	CH	CH	CH	CH	CH	CH	N
C	CH	CH	CH	N	CH	CH	CH
C	CH	CH	N	CH	CH	CH	CH
C	CH	CH	CH	CH	CH	N	CH
C	CH	CH	CH	CH	N	CH	CH
C	CH	N	CH	CH	CH	CH	CH
C	N	CH	CH	CH	CH	CH	CH
C	CH	CH	CH	O	CH_2	CH_2	O
C	CH	CH	CH	O	CH	CH	O
C	N	N	CH	CH	CH	CH	CH
C	CH	CH	CH	CH	N	N	CH
C	CH	CH	N	N	CH	CH	CH
C	CH	CH	CH	N	CH	CH	N
C	CH	CH	CH	CH	N	CH	N
C	CH	CH	CH	N	CH	N	CH
C	CH	CH	CH	CH	CH	N	N
C	CH	CH	CH	N	N	CH	CH
C	N	CH	N	N	CH	CH	N
N	CH	CH	S	CH	CH	CH	CH
O	CH	CH	CH	S	CH	CH	NH
C	CH	CH	CH	S	CH	CH	NMe
C	CH	CH	CH	NH	CH	CH	S
C	CH	CH	CH	NMe	CH	CH	S

N	CO	CH	CH	CH	CH	CH	CH
N	CH	CH	CO	CH	CH	CH	CH
C	CH	CH	CH	NH	CO	CH	CH
C	CH	CH	CH	NMe	CO	CH	CH
C	CH	CH	CH	CH	CH	CO	NH
C	CH	CH	CH	CH	CH	CO	NMe
C	CH	CH	CH	NH	CH	CH	CO
C	CH	CH	CH	NMe	CH	CH	CO
C	CH	CH	CH	CO	CH	CH	NH
C	CH	CH	CH	CO	CH	CH	NMe
C	CH	NH	CO	CH	CH	CH	CH
C	CH	NMe	CO	CH	CH	CH	CH
C	CH	CH	CH	CO	NH	CH	CH
C	CH	CH	CH	CO	NMe	CH	CH
C	CH	CH	CH	CH	CH	NH	CO
C	CH	CH	CH	CH	CH	NMe	CO
C	CO	NH	CH	CH	CH	CH	CH
C	CO	NMe	CH	CH	CH	CH	CH
C	NH	CO	CH	CH	CH	CH	CH
C	NMe	CO	CH	CH	CH	CH	CH
C	CH	CH	CH	CH	NH	CO	CH
C	CH	CH	CH	CH	NMe	CO	CH
C	CH	CH	CH	CH	CO	NH	CH
C	CH	CH	CH	CH	CO	NMe	CH
C	N	NH	CO	CH	CH	CH	CH
C	N	NMe	CO	CH	CH	CH	CH
C	CH	CH	CH	CH	N	NH	CO
C	CH	CH	CH	CH	N	NMe	CO
C	CH	CH	CH	CO	NH	N	CH
C	CH	CH	CH	CO	NMe	N	CH

Table 19

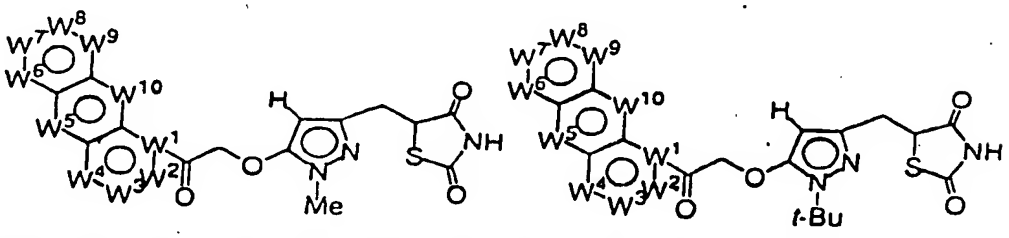


wherein W^1, W^2, W^3, W^4, W^5, W^6, W^7 and W^8 are as identified in the following Table.

W^1	W^2	W^3	W^4	W^5	W^6	W^7	W^8
CH	C	CH	CH	CH	CH	CH	CH
CH	C	CH	CH	CH	CH	CH	N
CH	C	CH	CH	N	CH	CH	CH
N	C	CH	CH	CH	CH	CH	CH
CH	C	CH	N	CH	CH	CH	CH
CH	C	CH	CH	CH	CH	N	CH
CH	C	CH	CH	CH	N	CH	CH
CH	C	N	CH	CH	CH	CH	CH
CH	C	CH	CH	O	CH_2	CH_2	O
CH	C	CH	CH	O	CH	CH	O
CH	C	CH	CH	CH	N	N	CH
CH	C	CH	N	N	CH	CH	CH
N	C	CH	CH	CH	CH	CH	N
N	C	CH	N	CH	CH	CH	CH
CH	C	CH	CH	N	CH	CH	N
N	C	N	CH	CH	CH	CH	CH
CH	C	CH	CH	CH	N	CH	N
CH	C	CH	CH	N	CH	N	CH
CH	C	N	N	CH	CH	CH	CH
CH	C	CH	CH	CH	CH	N	N
CH	C	CH	CH	N	N	CH	CH
N	C	N	CH	N	CH	CH	N
N	C	CH	N	CH	N	CH	N
N	C	CH	N	N	CH	N	CH
S	C	CH	NH	CH	CH	CH	CH
S	C	CH	NMe	CH	CH	CH	CH
NH	C	CH	S	CH	CH	CH	CH
NMe	C	CH	S	CH	CH	CH	CH
CH	C	CH	CH	NH	CH	CH	S
CH	C	CH	CH	NMe	CH	CH	S
CH	C	CH	CH	S	CH	CH	NH
CH	C	CH	CH	S	CH	CH	NMe
S	C	CMe	NH	CH	CH	CH	CH
S	C	CMe	NMe	CH	CH	CH	CH
CH	C	CO	NH	CH	CH	CH	CH
CH	C	CO	NMe	CH	CH	CH	CH
CH	C	CH	CH	NH	CO	CH	CH
CH	C	CH	CH	NMe	CO	CH	CH
CH	C	CH	CH	CH	CH	CO	NH
CH	C	CH	CH	CH	CH	CO	NMe
NH	C	CH	CO	CH	CH	CH	CH
NMe	C	CH	CO	CH	CH	CH	CH
CO	C	CH	NH	CH	CH	CH	CH
CO	C	CH	NMe	CH	CH	CH	CH
CO	N	CH	CH	CH	CH	CH	CH
CH	C	NH	CO	CH	CH	CH	CH
CH	C	NMe	CO	CH	CH	CH	CH
CH	C	CH	CH	CO	NH	CH	CH

CH	C	CH	CH	CO	NMe	CH	CH
CH	C	CH	CH	CH	CH	NH	CO
CH	C	CH	CH	CH	CH	NMe	CO
CH	N	CO	CH	CH	CH	CH	CH
CH	C	CH	CH	CH	CO	NH	CH
CH	C	CH	CH	CH	CO	NMe	CH
CH	C	CH	CH	CH	NH	CO	CH
CH	C	CH	CH	CH	NMe	CO	CH
CO	N	N	CH	CH	CH	CH	CH
CH	C	CH	CH	CH	N	NH	CO
CH	C	CH	CH	CH	N	NMe	CO
CH	C	CH	CH	CO	NH	N	CH
CH	C	CH	CH	CO	NMe	N	CH

Table 20



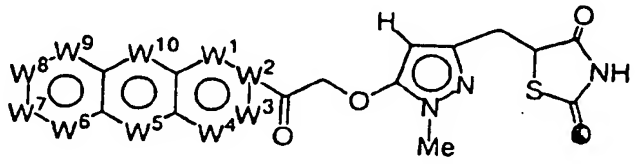
wherein W^1, W^2, W^3, W^4, W^5, W^6, W^7, W^8, W^9 and W^{10} are as identified in the following Table.

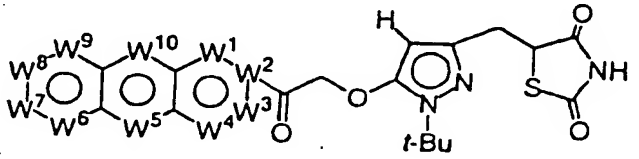
W^1	W^2	W^3	W^4	W^5	W^6	W^7	W^8	W^9	W^{10}
C	CH	CH	CH	O	CH	CH	CH	CH	CH_2
C	CH	CH	CH	CH_2	CH	CH	CH	CH	O
C	CH	CH	CH	O	CH	CH	CH	CH	S
C	CH	CH	CH	S	CH	CH	CH	CH	O
C	CH	CH	CH	S	CH	CH	CH	CH	S
C	CH	CH	CH	N	CH	CH	CH	CH	CH
C	CH	CH	CH	CH	CH	CH	CH	CH	N
C	CH	CH	CH	N	CH	CH	CH	CH	N
C	CH	CH	CH	S	CH	CH	CH	CH	NH
C	CH	CH	CH	S	CH	CH	CH	CH	NMe
C	CH	CH	CH	NH	CH	CH	CH	CH	S
C	CH	CH	CH	NMe	CH	CH	CH	CH	S
C	CH	CH	CH	O	CH	CH	CH	CH	NH
C	CH	CH	CH	NH	CH	CH	CH	CH	O
C	CH	CH	N	O	CH	CH	CH	CH	CH_2
C	CH	CH	CH	O	N	CH	CH	CH	CH_2
C	CH	CH	CH	CH_2	CH	CH	CH	N	O
C	CH	CH	N	O	CH	CH	CH	CH	CO
C	CH	CH	CH	O	N	CH	CH	CH	CO

C	CH	CH	CH	CO	CH	CH	CH	N	O
C	CH	CH	CH	-*	CH	CH	CH	CH	CH_2
C	CH	CH	CH	CH_2	CH	CH	CH	CH	-
C	CH	CH	CH	-	CH	CH	CH	CH	NH
C	CH	CH	CH	-	CH	CH	CH	CH	NMe
C	CH	CH	CH	NH	CH	CH	CH	CH	-
C	CH	CH	CH	NMe	CH	CH	CH	CH	-

*: covalent bond

Table 21





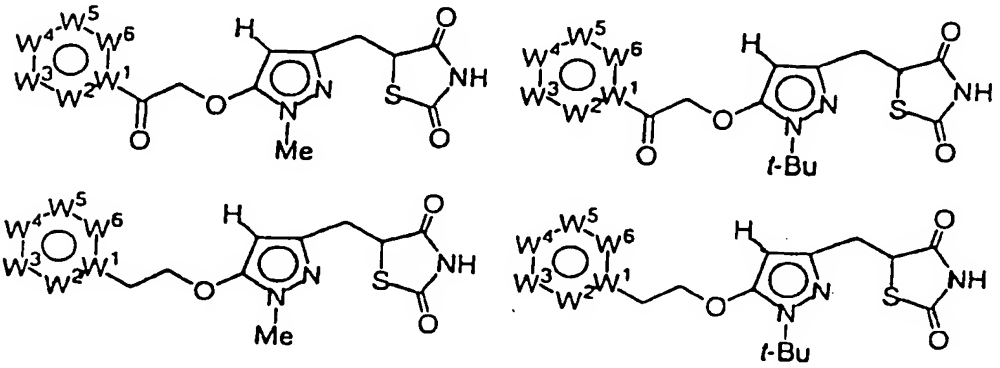
wherein W^1, W^2, W^3, W^4, W^5, W^6, W^7, W^8, W^9 and W^{10} are as identified in the following Table.

W^1	W^2	W^3	W^4	W^5	W^6	W^7	W^8	W^9	W^{10}
CH	C	CH	CH	O	CH	CH	CH	CH	CH_2
CH	C	CH	CH	CH_2	CH	CH	CH	CH	O
CH	C	CH	CH	O	CH	CH	CH	CH	S
CH	C	CH	CH	S	CH	CH	CH	CH	O
CH	C	CH	CH	S	CH	CH	CH	CH	S
CH	C	CH	CH	N	CH	CH	CH	CH	CH
CH	C	CH	CH	CH	CH	CH	CH	CH	N
CH	C	CH	CH	N	CH	CH	CH	CH	N
CH	C	CH	CH	S	CH	CH	CH	CH	NH
CH	C	CH	CH	S	CH	CH	CH	CH	NMe
CH	C	CH	CH	NH	CH	CH	CH	CH	S
CH	C	CH	CH	NMe	CH	CH	CH	CH	S
CH	C	CH	CH	O	CH	CH	CH	CH	NH
CH	C	CH	CH	NH	CH	CH	CH	CH	O
CH	C	CH	N	O	CH	CH	CH	CH	CH_2

N	C	CH	CH	CH_2	CH	CH	CH	CH	O
CH	C	CH	CH	O	N	CH	CH	CH	CH_2
CH	C	CH	CH	CH_2	CH	CH	CH	N	O
CH	C	CH	N	O	CH	CH	CH	CH	CO
N	C	CH	CH	CO	CH	CH	CH	CH	O
CH	C	CH	CH	O	N	CH	CH	CH	CO
CH	C	CH	CH	CO	CH	CH	CH	N	O
CH	C	CH	CH	-*	CH	CH	CH	CH	CH_2
CH	C	CH	CH	CH_2	CH	CH	CH	CH	-
CH	C	CH	CH	-	CH	CH	CH	CH	NH
CH	C	CH	CH	-	CH	CH	CH	CH	NMe
CH	C	CH	CH	NH	CH	CH	CH	CH	-
CH	C	CH	CH	NMe	CH	CH	CH	CH	-
CH	C	CMe	N	O	CH	CH	CH	CH	CO
CH	C	CMe	N	O	CH	CH	CMe	CH	CO

*: covalent bond

Table 22



wherein W^1, W^2, W^3, W^4, W^5 and W^6 are as identified in the following Table.

W^1	W^2	W^3	W^4	W^5	W^6
C	CH	CH	CH	CH	CH
C	CMe	CH	CH	CH	CH
C	CH	CMe	CH	CH	CH
C	CH	CH	CMe	CH	CH
C	CEt	CH	CH	CH	CH
C	CH	CEt	CH	CH	CH
C	CH	CH	CEt	CH	CH
C	C^iPr	CH	CH	CH	CH
C	CH	C^iPr	CH	CH	CH
C	CH	CH	C^iPr	CH	CH
C	C^tBu	CH	CH	CH	CH
C	CH	C^tBu	CH	CH	CH
C	CH	CH	C^tBu	CH	CH
C	COMe	CH	CH	CH	CH
C	CH	COMe	CH	CH	CH
C	CH	CH	COMe	CH	CH
C	CCl	CH	CH	CH	CH
C	CH	CCl	CH	CH	CH
C	CH	CH	CCl	CH	CH
C	CF	CH	CH	CH	CH
C	CH	CF	CH	CH	CH
C	CH	CH	CF	CH	CH
C	CBr	CH	CH	CH	CH
C	CH	CBr	CH	CH	CH
C	CH	CH	CBr	CH	CH
C	COH	CH	CH	CH	CH
C	CH	OH	CH	CH	CH
C	CH	CH	COH	CH	CH
C	COBn	CH	CH	CH	CH
C	CH	COBn	CH	CH	CH
C	CH	CH	COBn	CH	CH
C	COPh	CH	CH	CH	CH
C	CH	COPh	CH	CH	CH
C	CH	CH	COPh	CH	CH
C	CPh	CH	CH	CH	CH
C	CH	CPh	CH	CH	CH
C	CH	CH	CPh	CH	CH
C	CNH_2	CH	CH	CH	CH
C	CH	CNH_2	CH	CH	CH
C	CH	CH	CNH_2	CH	CH
C	$CNMe_2$	CH	CH	CH	CH
C	CH	$CNMe_2$	CH	CH	CH
C	CH	CH	$CNMe_2$	CH	CH
C	CNO_2	CH	CH	CH	CH
C	CH	CNO_2	CH	CH	CH
C	CH	CH	CNO_2	CH	CH
C	CCN	CH	CH	CH	CH
C	CH	CCN	CH	CH	CH

C	CH	CH	CCN	CH	CH
C	CMe	CPh	CH	CH	CH
C	CMe	CH	CPh	CH	CH
C	CMe	CH	CH	CPh	CH
C	CMe	CH	CH	CH	CPh
C	CPh	CMe	CH	CH	CH
C	CH	CMe	CPh	CH	CH
C	CH	CMe	CH	CPh	CH
C	CH	CMe	CH	CH	CPh
C	CPh	CH	CMe	CH	CH
C	CH	CPh	CMe	CH	CH
C	CH	CH	CMe	CPh	CH
C	CH	CH	CMe	CH	CPh
C	CMe	CMe	CH	CH	CH
C	CMe	CH	CMe	CH	CH
C	CMe	CH	CH	CMe	CH
C	CMe	CH	CH	CH	CMe
C	CH	CMe	CMe	CH	CH
C	CH	CMe	CH	CMe	CH
C	COMe	COMe	CH	CH	CH
C	COMe	CH	COMe	CH	CH
C	COMe	CH	CH	COMe	CH
C	COMe	CH	CH	CH	COMe
C	CH	COMe	OMe	CH	CH
C	CH	COMe	CH	COMe	CH
C	N	CH	CH	CH	CH
C	CH	N	CH	CH	CH
C	CH	CH	N	CH	CH
N	CH	CH	CH	CH	CO
N	CPh	CH	CH	CH	CO
N	CH	CPh	CH	CH	CO
N	CH	CH	CPh	CH	CO
N	CH	CH	CH	CPh	CO
N	CMe	CH	CH	CH	CO
N	CH	CMe	CH	CH	CO
N	CH	CH	CMe	CH	CO
N	CH	CH	CH	CMe	CO
N	CCN	CH	CH	CH	CO
N	CH	CCN	CH	CH	CO
N	CH	CH	CCN	CH	CO
N	CH	CH	CH	CCN	CO
C	N	CMe	CO	CH	CH
C	N	CH	CMe	CH	CH
C	N	CH	CH	CMe	CH
C	N	CH	CH	CH	CMe
C	CMe	N	CH	CH	CH
C	CH	N	CMe	CH	CH
C	CH	N	CH	CMe	CH
C	CH	N	CH	CH	CMe
C	CMe	CH	N	CH	CH
C	CH	CMe	N	CH	CH
C	N	CEt	CH	CH	CH
C	N	CH	CEt	CH	CH

C	N	CH	CH	CEt	CH
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C	CH	CEt	N	CH	CH
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C	CH	N	CH	CCl	CH
C	CH	N	CH	CH	CH
C	CH	CH	CH	CH	CCl
C	CCl	N	N	CH	CH
C	CH	N	N	CH	CH
C	N	N	N	CH	CH
C	N	N	CH	CF	CH
C	N	CH	CCl	CH	CH
C	CF	CF	CH	CH	CH
C	CH	CH	CH	CF	CH
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C	CH	N	N	CH	CF
C	CF	N	N	CH	CH
C	CH	N	N	CH	CH
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C	N	COMe	CH	CH	CH
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C	N	CH	N	CH	CH
C	COMe	CH	N	CH	CH
C	CH	CH	N	CH	CH
C	CH	COMe	N	CH	CH
C	CH	CH	CH	COMe	CH
C	COMe	COPh	CH	CH	CH
C	CH	CH	CH	CH	CH
C	N	CH	N	CH	CH
C	N	N	N	CH	CH
C	N	N	N	COMe	CH
C	N	N	CH	CH	CH
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C	CH	CH	N	CH	CH
C	CH	N	N	CH	CH
C	COPh	N	N	CH	CH
C	CH	N	N	COPh	CH
C	N	CH	CH	CH	CH
C	N	COBn	CH	CH	CH
C	N	CH	CH	CH	CH
C	N	CH	CH	CH	CH
C	COBn	N	CH	COBn	CH
C	CH	N	CH	CH	CH
			CH	CH	CH
			COBn	CH	CH

C	CH	N	CH	COBn	CH
C	CH	N	CH	CH	COBn
C	COBn	CH	N	CH	CH
C	CH	COBn	N	CH	CH
C	N	CPh	CH	CH	CH
C	N	CH	CPh	CH	CH
C	N	CH	CH	CPh	CH
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C	CPh	N	CH	CH	CH
C	CH	N	CPh	CH	CH
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C	CH	N	CH	CH	CPh
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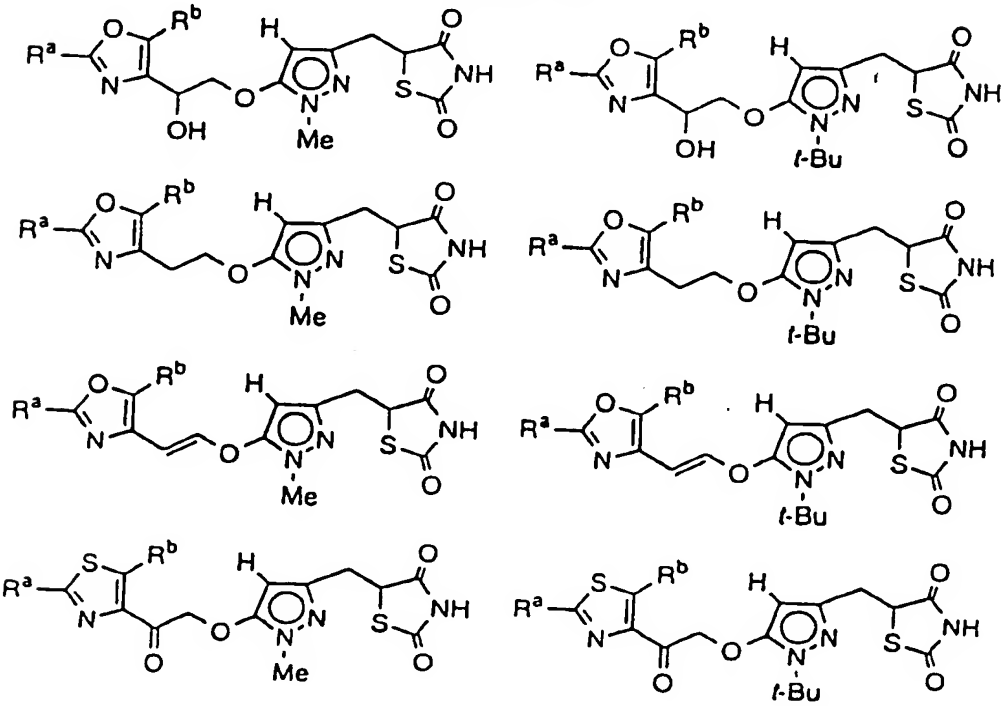
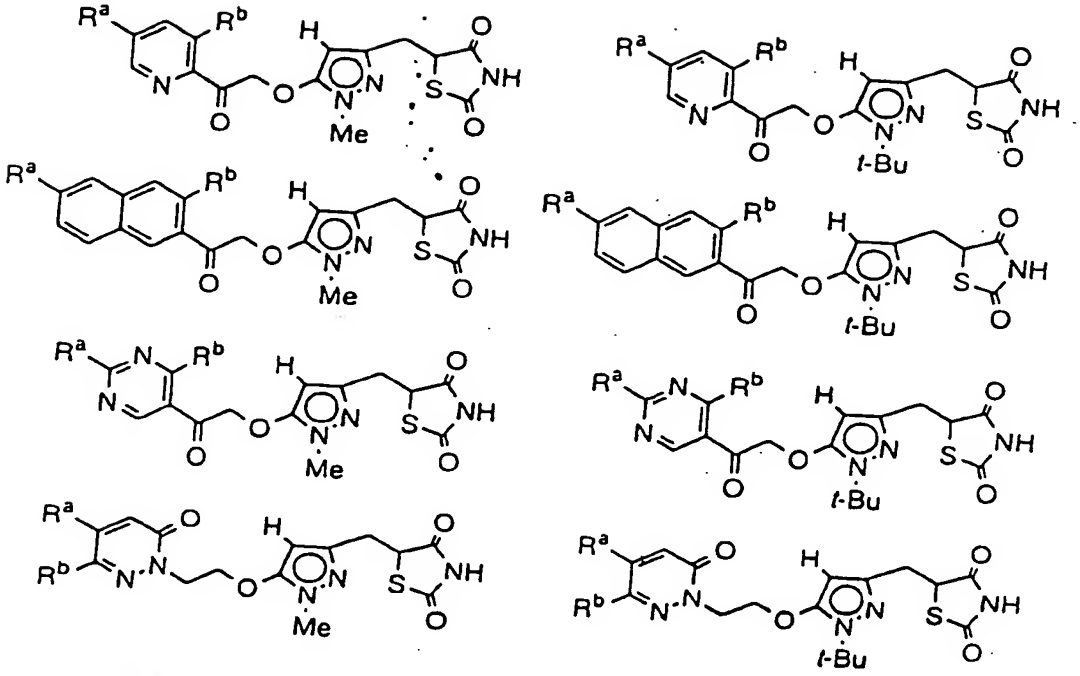
C	CH	CPh	N	CH	CH
C	N	CCN	CH	CH	CH
C	N	CH	CCN	CH	CH
C	N	CH	CH	CCN	CH
C	N	CH	CH	CH	CCN
C	CCN	N	CH	CH	CH
C	CH	N	CCN	CH	CH
C	CH	N	CH	CCN	CH
C	CH	N	CH	CH	CCN
C	CCN	CH	N	CH	CH
C	CH	CCN	N	CH	CH
C	N	CH	CH	CH	N
C	N	CH	N	CH	CH
C	CH	N	N	CH	CH
C	CH	N	CH	N	CH
C	N	CH	CH	N	CH
C	N	N	CH	CH	CH

Table 23





wherein R^a and R^b are as identified in the following Table.

R^a	R^b	R^a	R^b	R^a	R^b
H	Me	Q81	Me	Q18	Me
Me	Me	Q82	Me	Q14	Me
Et	Me	Q83	Me	Q45	Me
^{n}Pr	Me	Q10	Me	Q72	Me
^{i}Pr	Me	Q7	Me	Q13	Me
^{t}Bu	Me	Q84	Me	OPh	Me
^{c}Pr	Me	Q85	Me	Q79	Me
^{c}Hex	Me	Q8	Me	Ph	H
Q80	Me	Q9	Me	Ph	Me
Ph	Me	Q86	Me	Ph	Et
Q1	Me	Q87	Me	Ph	^{n}Pr
Q2	Me	Q88	Me	Ph	^{i}Pr
Q3	Me	4-Ph-Ph	Me	Ph	^{t}Bu
Q4	Me	Q11	Me	Ph	^{c}Pr
Q5	Me	Q12	Me	Ph	^{c}Hex
Q6	Me	Q17	Me	Ph	Ph

The compound of the above formula (I) of the present

invention has acidic hydrogen on a thiazolidine ring or on an oxazolidine ring. Further, when substituent Z is a heterocyclic aromatic group or a heterocyclicaliphatic group, it sometimes has a basic nitrogen. Such a compound may be converted to a pharmaceutically acceptable non-toxic salt with an appropriate base or acid, if desired. The compound of the formula (I) can be used for the purpose of the present invention either in the free form or in the form of a pharmaceutically acceptable salt. Examples of the basic salt include an alkali metal salt (lithium salt, sodium salt, potassium salt and the like), an alkali earth metal salt (calcium salt, magnesium salt and the like), an aluminum salt, an ammonium salt which may be unsubstituted or substituted with a methyl, ethyl or benzyl group, an organic amine salt (methylamine salt, ethylamine salt, dimethylamine salt, diethylamine salt, trimethylamine salt, triethylamine salt, cyclohexylamine salt, ethylenediamine salt, bicyclohexylamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, piperazine salt, dibenzylpiperidine salt, dehydroabietilamine salt, N,N'-bisdehydroabietilamine salt, benzathine(N,N'-dibenzylethylenediamine) salt, glucamine salt, meglumine(N-methylglucamine) salt, benetamine(N-benzylphenetylamine)salt, trometamine(2-amino-2-hydroxymethyl-1,3-propanediol)salt, choline salt, procaine salt), a basic amino acid salt (lysine salt,

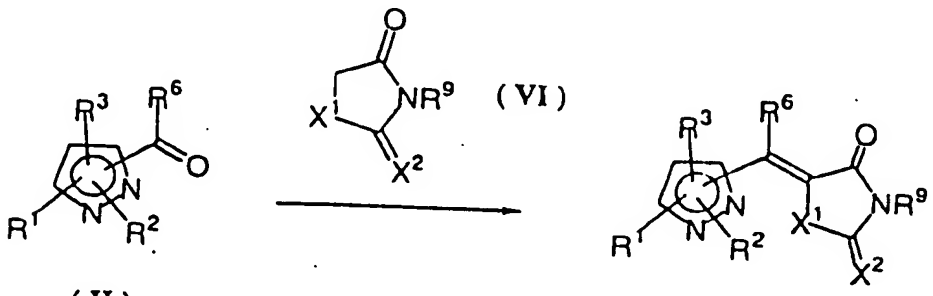
ornithine salt, arginine salt and the like), a pyridine salt, a collidine salt, a quinoline salt, and the like. Examples of an acid-addition salt include a mineral acid salt (hydrochloride, hydrobromide, sulfate, hydrogensulfate, nitrate, phosphate, hydrogenphosphate, dihydrogenphosphate and the like), an organic acid salt (formate, acetate, propionate, succinate, malonate, oxalate, maleate, fumarate, malate, citrate, tartrate, lactate, glutamate, asparate, picrate, carbonate and the like), a sulfonic acid salt (methanesulfonate, benzenesulfonate, toluenesulfonate and the like), and the like. Each of these salts can be prepared by a known method.

The compound having the formula (I), i.e. pyrazole type thiazolidines, can be prepared by the following synthetic methods.

A reaction solvent used in the preparation is stable under the reaction conditions, and is preferably so inert as not to inhibit the reaction. Examples of the reaction solvent include water, alcohols (such as methanol, ethanol, propanol, butanol and octanol), cellosolves (such as methoxyethanol and ethoxyethanol), aprotic polar organic solvents (such as dimethylformamide, dimethylsulfoxide, dimethylacetamide, tetramethylurea, sulfolane and N,N-dimethylimidazolidinone), ethers (such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane), aliphatic hydrocarbons (such as pentane, n-

hexane, c-hexane, octane, decaline and petroleum ether), aromatic hydrocarbons (such as benzene, chlorobenzene, nitrobenzene, toluene, xylene and tetralin), halogenated hydrocarbons (such as chloroform, dichloromethane and dichloroethane), ketones (such as acetone, methyl ethyl ketone and methyl butyl ketone), lower aliphatic acid esters (such as methyl acetate, ethyl acetate and methyl propionate), alkoxy alkanes (such as dimethoxyethane and diethoxyethane), acetonitrile, and the like. These solvents are optionally selected depending on the reactivity of the aimed reaction, and are respectively used alone or in a mixture. In some cases, there are used as a non-aqueous solvent by using a dehydrating agent or a drying agent. The above-mentioned solvents are merely examples which can be used in the reaction of the present invention, and the present invention is not limited to these conditions.

Process 1



(II) (VI) (I-1)

(wherein R^1, R^2, R^3, R^6, X^1 and X^2 are as defined above, and R^9 is a hydrogen atom or a protecting group of amide (such as Tr: trityl)).

A compound wherein R^4 and R^7 are bonded together in the formula (I), i.e. a compound of the formula (I-1), can be obtained by dehydration-condensation of a compound of the formula (II) and a compound of the formula (VI). The compound of the formula (VI) is a well known compound or can be synthesized by the method disclosed in "J. Prakt. Chem." (vol. 2, p. 253, 1909), "J. Prakt. Chem." (vol. 3, p. 45, 1919), "Chem. Ber." (vol. 118, p. 774, 1985), and German Laid Open Patent Publication No. DE-3045059. The compound of the formula (VI) wherein R^9 is hydrogen, can be used in this reaction after protecting its acidic amideproton at the 3-position of thiazolidine or oxazolidine with an appropriate substituent (such as TR: trityl) by a well known method.

This reaction is conducted usually in an appropriate organic solvent in the presence of base or acid. Examples of such a solvent include alcohols, cellosolves, aprotic polar organic solvents, ethers, aromatic hydrocarbons, halogenated hydrocarbons, alkoxyalkanes and acetonitrile.

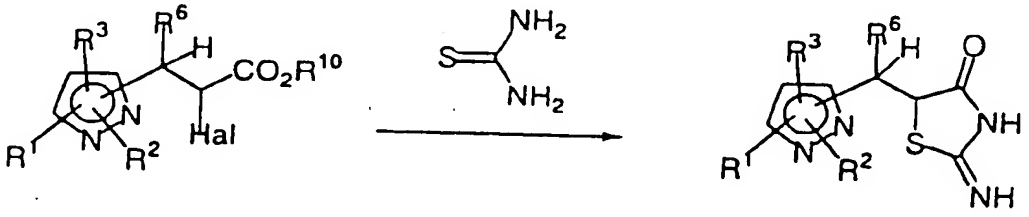
Examples of the base and the acid include organic amines (such as dimethylamine, diethylamine, diisopropylamine, diisopropylethylamine, trimethylamine, triethylamine, piperidine, piperazine, pyrrolidine, morpholine, pyridine, methanolamine and ethanolamine), metal alkoxides (such as sodium methoxide, sodium ethoxide and lithium isopropoxide), inorganic alkali

metal salts (such as potassium carbonate, sodium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydride, sodium acetate and potassium acetate), organic acids (such as acetic acid, trichloroacetic acid and trifluoroacetic acid), inorganic acids (such as phosphoric acid), and the like. These materials are selected appropriately depending on the reactivity of the aimed reaction.

This reaction can be accelerated by removing water formed during reaction out of the system by using an appropriate dehydrating agent such as molecular sieves and anhydrous sodium sulfate or by azeotropic distillation using Dean-Stark tube.

This reaction is conducted usually at a temperature ranging from 0°C to a boiling point of a solvent used, preferably from 20°C to 120°C, for from 0.5 to 30 hours.

Process 2



(VII) (I-2e) (X^1=S, X^2=NH)

(wherein R^1, R^2, R^3 and R^6 are as defined above, R^{10} is C_1-C_4 alkyl such as methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl, and Hal is a chlorine atom, a bromine atom or an iodine atom).

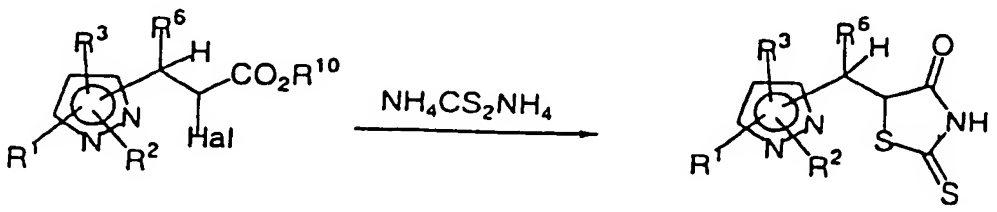
A compound of the formula (I) wherein R^4 and R^7 are hydrogen, X^1 is S and X^2 is NH, i.e. a compound of the formula (I-2e) (R^4, R^7=H, X^1=S, X^2=NH), can be obtained by reacting thiourea with a halocarboxylic acid ester of the formula (VII).

This reaction is conducted usually in an appropriate organic solvent in the presence of base or acid. Examples of the solvent used include alcohols, cellosolves and aprotic polar organic solvents, and preferably sulfolane is used.

This reaction is conducted usually at a temperature ranging from 0°C to a boiling point of a solvent used, preferably from 50°C to 150°C, for 0.5 to 10 hours.

During the reaction, hydrogen halide is by-produced, but can be captured with an appropriate base to accelerate the reaction. Examples of the base thus used include organic amines (such as dimethylamine, diethylamine, diisopropylamine, diisopropylethylamine, trimethylamine, triethylamine, piperidine, piperazine, pyrrolidine, morpholine, pyridine, methanolamine and ethanolamine), inorganic alkali metal salts (such as sodium acetate and potassium acetate), and the like.

Process 3



(VII) (I-2b) (X^1=S, X^2=S)

(wherein R^1, R^2, R^3, R^6, R^{10} and Hal are as defined above).

A compound of the formula (I) wherein R^4 and R^7 are H, and X^1 and X^2 are S, i.e. a compound of the formula (I-2b) (R^4, R^7=H, X^1, X^2=S), can be obtained by reacting ammonium dithiocarbamate with a halocarboxylic acid ester of the formula (VII) and by treating the compound with acid.

This reaction is conducted usually in water or an appropriate organic solvent, or in a mixture thereof. Examples of the solvent thus used include alcohols, cellosolves and aprotic polar organic solvents.

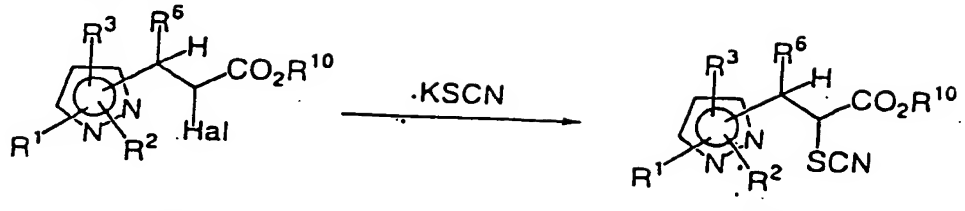
This reaction is conducted usually at a temperature ranging from -10°C to 50°C, preferably from 0°C to 30°C, for 0.5 to 50 hours.

During this reaction, hydrogen halide is by-produced, but can be captured with an appropriate base to accelerate the reaction. Examples of the base thus used include organic amines (such as dimethylamine, diethylamine, diisopropylamine, diisopropylethylamine, trimethylamine, triethylamine, piperidine, piperazine, pyrrolidine, morpholine, pyridine, methanolamine and ethanolamine), inorganic alkali metal salts (such as potassium carbonate, sodium carbonate, sodium acetate and potassium acetate), and the like.

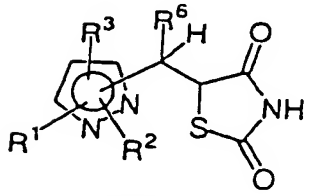
The adduct thus obtained is treated with an acid (such as hydrochloric acid) to obtain a compound of the

formula (I-2b).

Process 4



(VII) (VIII)



(I-2a)
(X^1=S, X^2=O)

(wherein R^1, R^2, R^3, R^6, R^{10} and Hal are as defined above).

A compound of the formula (I) wherein R^4 and R^7 are H, X^1 is S and X^2 is O, i.e. a compound of the formula (I-2a) (R^4, R^7=H, X^1=S, X^2=O), can be obtained by reacting an alkalithiocyanate (such as potassium thiocyanate or sodium thiocyanate) with a halocarboxylic acid ester of the formula (VII) to prepare a compound of the formula (XIII) and by treating the compound with an acid.

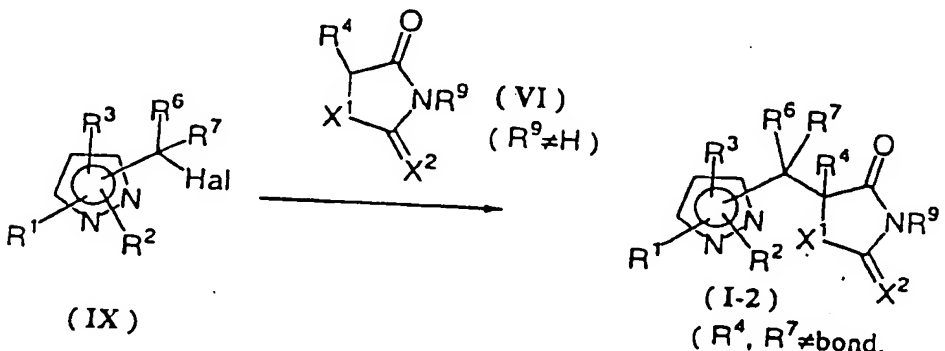
This reaction is conducted usually in an appropriate organic solvent. Examples of the solvent thus used include aprotic polar organic solvents.

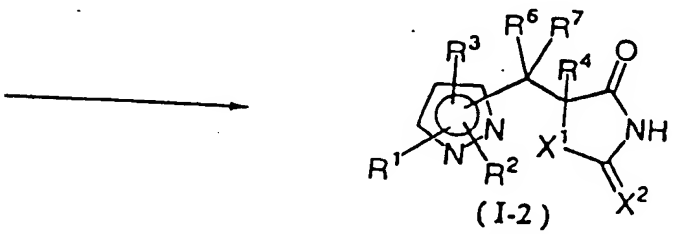
This reaction is conducted usually at a temperature ranging from 50°C to 150°C, preferably from 80°C to

120°C, for 0.5 to 10 hours.

A compound of the formula (XIII) is isolated, or it is further subjected to acid treatment in the reaction system without being isolated therefrom to obtain the aimed compound of the formula (I-2a). Examples of the acid thus used include hydrochloric acid, and the acid treatment is conducted in an alcohol or an aprotic polar organic solvent. This reaction is conducted at a temperature of from 50°C to 150°C, preferably from 70°C to 100°C, for 5 to 50 hours.

Process 5





(wherein R^1, R^2, R^3, R^4, R^6, R^7, R^9, X^1, X^2 and Hal are as defined above).

A compound of the formula (I) other than the one

wherein R^4 and R^7 together form a bond, i.e. a compound of the formula (I-2), can be obtained by reacting a compound of the formula (VI) with a halomethylpyrazole of the formula (IX). The compound of the formula (VI) used herein is a well known compound or can be synthesized by a method disclosed in "Ukr. Khim. Zh." (vol. 16, p. 545, 1950), "J. Med. Chem." (vol. 34, p. 1538, 1991), "J. Prakt. Chem." (vol. 2, 79, P. 259 (1909), "J. Prakt. Chem." (vol. 2, 99, P. 56 (1919) or Japanese Unexamined Patent Publication No. 216882/1984. The compound of the formula (VI) wherein R^9 is hydrogen, is used in this reaction preferably after protecting its acidic amide proton with an appropriate substituent (such as Tr: trityl) by a known method.

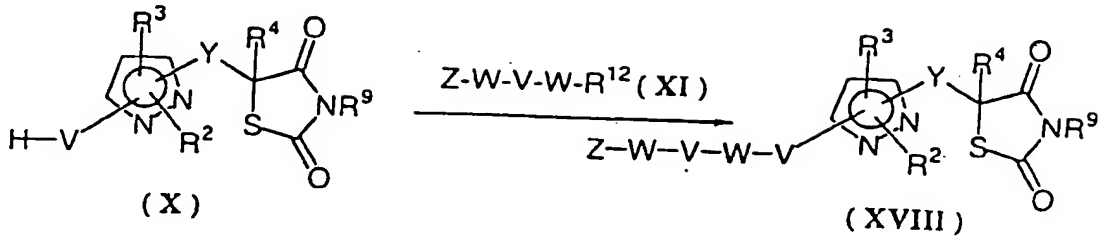
This reaction is conducted usually in an appropriate organic solvent in the presence of base. Examples of the solvent thus used include aprotic polar organic solvents, ethers and alkoxyalkanes. Examples of the base thus used include a strong base such as alkali metal amides (e.g. sodium amide and potassium amide). These materials are selected optionally depending on the reactivity of the aimed reaction.

Also, this reaction can be conducted in accordance with a method disclosed in "J. Amer. Chem. Soc." (vol. 87, p. 4588, 1965) or "J. Med. Chem." (vol. 34, p. 1538, 1991). In such a case, a compound of the formula (VI) is reacted with magnesium methylcarbonate in an inert gas

atmosphere such as nitrogen and in an aprotic polar organic solvent such as dimethylformamide to form a chelate compound, and the chelate compound thus formed is further reacted with a halomethylpyrazole of the formula (IX) to obtain a compound of the formula (I-2). This reaction is conducted usually at a temperature ranging from 20°C to 150°C, preferably from 70°C to 100°C. The reaction time varies depending on the materials used, but the formation of the chelate compound takes from 0.5 to 2 hours and the reaction with the halomethylpyrazole takes from 0.5 to 5 hours.

In some cases, an amide group at the 3-position of thiazolidine of the compound of the formula (I-2) thus obtained may be deprotected by a well-known method. When R^9 is Tr (trityl), this method is conducted by using an organic acid such as trifluoroacetic acid and trichloroacetic acid or an inorganic acid such as hydrochloric acid and sulfuric acid. This reaction is conducted in the absence of a solvent or in the presence of a solvent such as ethers including tetrahydrofuran and dioxane and halogenated solvents including chloroform and dichloromethane, at a temperature ranging from 0°C to 100°C, preferably from 10°C to 50°C, for 0.1 to 5 hours.

Process 6

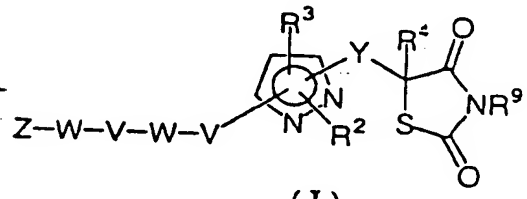


(X)

(X-1;Y=CR6R7and R4,R7=bond
X-2;Y=CR6R7and R4,R7=H)

(XVIII)

(I-1a;Y=CR6R7and R4,R7=bond
I-2a;Y=CR6R7and R4,R7=H
R9≠H)



(I)

(I-1a;Y=CR6R7and R4,R7=bond
I-2a;Y=CR6R7and R4,R7=H
R9=H)

(wherein R^2, R^3, R^4, R^9, V, W, Y and Z are as defined above, and R^{12} is an appropriate leaving group in nucleophilic substitution reaction, examples of which include a halogen such as chlorine, bromine and iodine, and an aromatic or aliphatic sulfonyloxy group such as p-toluenesulfonyloxy, benzenesulfonyloxy and methanesulfonyloxy).

Among compounds of formula (I), a compound wherein R^1 is -V-W-Z and W is $COCH_2$, can be obtained by using a compound of Z-$COCH_2$-Hal (W=$COCH_2$, R^{12}=Hal, Z and Hal are substituents explained above) instead of the formula (XI). Such a compound is well known and is commercially

available, or can be obtained by a well known method (for example, British Laid Open Patent Publication No. 1107677 discloses a compound wherein Z is pyrrole, Japanese Unexamined Patent Publication No. 85372/1986 discloses a compound wherein Z is oxazole or thiazole and U.S. Patent No. 4,167,626 discloses a compound wherein Z is triazole). Also, such a compound can be obtained by halogenating Z-$COCH_3$ (for example, "Bull. Soc. Chim. Fr., p. 1760 (1973)" discloses a compound wherein Z is furan, "Tetrahedron, 29(2), p. 413 (1973)" discloses a compound wherein Z is thiophene, "J. Heterocyclic Chem., 27(5), p. 1209 (1990)" discloses a compound wherein Z is pyrrole, "Bull. Soc. Chim. Fr., p. 540 (1988)", "Bull. Soc. Chim. Fr., p. 318 (1987)", "J. Heterocyclic Chem., 23(1), P. 275 (1986)", "Arch. Pharm., 316(7), p. 608 (1983)" and "Synlett., (7), p. 483 (1991)" disclose a compound wherein Z is pyrazole, "J. Heterocyclic Chem., 17(8), p. 1723 (1980)" discloses a compound wherein Z is imidazole, and "J. Chem. Soc. C(20), p. 2005 (1976)" and "Heterocycles, 26(3), p. 745 (1987)" disclose a compound wherein Z is triazole) as a starting material by means of an appropriate well known halogenation method (e.g. a method disclosed in Japanese Unexamined Patent Publication No. 85372/1986). Also, such a compound can be obtained by subjecting Z-CO_2R' (R'=lower alkyl or substituted or unsubstituted benzyl) (for example, "Z. Chem., 9(1), p. 22 (1969)" and "Synth. Commun., 20(16),

p. 2537 (1990)" disclose a compound wherein Z is thiophene, "J. Org. Chem., 55(15), p. 4735 (1990)" and "Chem. Pharm. Bull., 17(3), p. 582 (1969)" disclose a compound wherein Z is pyrrole, European Laid Open Patent Publication No. 506194 discloses a compound wherein Z is imidazole, and "Chem. Ber., 117(3), p. 1194 (1984)" discloses a compound wherein Z is pyrazole or triazole) as a starting material to an appropriate well known reduction-oxidation reaction (for example, reduction by diisobutyl aluminum hydride and then oxidation by manganese dioxide) to obtain Z-CHO, and further by converting the product thus obtained to Z-$COCH_2$-hal by an appropriate method (e.g. a method disclosed in "Tetrahedron Letters, p. 4661 (1972)").

Among compounds of formula (I), a compound wherein R^1 is -O-W-$N(R^8)$-Z and W is CH_2CH_2, can be obtained by using a compound of Z-$N(R^8)$-CH_2CH_2-R^{12} (W=CH_2CH_2, R^{12} is a substituent explained above) among the compounds of the formula (XI). Such a compound is well known and is commercially available, or can be obtained by a well known method, for example, by a method disclosed in J. Med. Chem., 1994, vol., 37, p3980.

A compound of the formula (I) can also be obtained by reacting a compound of the formula (XI) with a hydroxyl group, a thiol group or an amino group of a compound of the formula (X) by nucleophilic substitution reaction. The compound of the formula (X) is preferably protected

by substituting hydrogen of R^9 with an appropriate substituent (e.g. Tr: trityl).

This reaction is usually conducted in an appropriate organic solvent in the presence of base. Examples of the solvent used include aprotic polar organic solvents, ethers, aromatic hydrocarbons, hydrogenated hydrocarbons, alkoxyalkanes, acetonitrile, and the like.

Examples of the base thus used include organic amines (such as dimethylamine, diethylamine, diisopropylamine, diisopropylethylamine, trimethylamine, triethylamine, piperidine, piperazine, pyrrolidine, morpholine, pyridine, methanolamine and ethanolamine), Acid Captor H: 3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one and Acid Captor 9M: 9-methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one), metal alkoxides (such as sodium methoxide, sodium ethoxide, lithium isopropoxide and potassium t-butoxide), inorganic alkali metal salts (such as sodium hydroxide, potassium hydroxide, lithium hydroxide, potassium carbonate, sodium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydride, sodium acetate and potassium acetate), and alkali metal amides (such as sodium amide). These materials are selected appropriately depending on the reactivity of the aimed reaction.

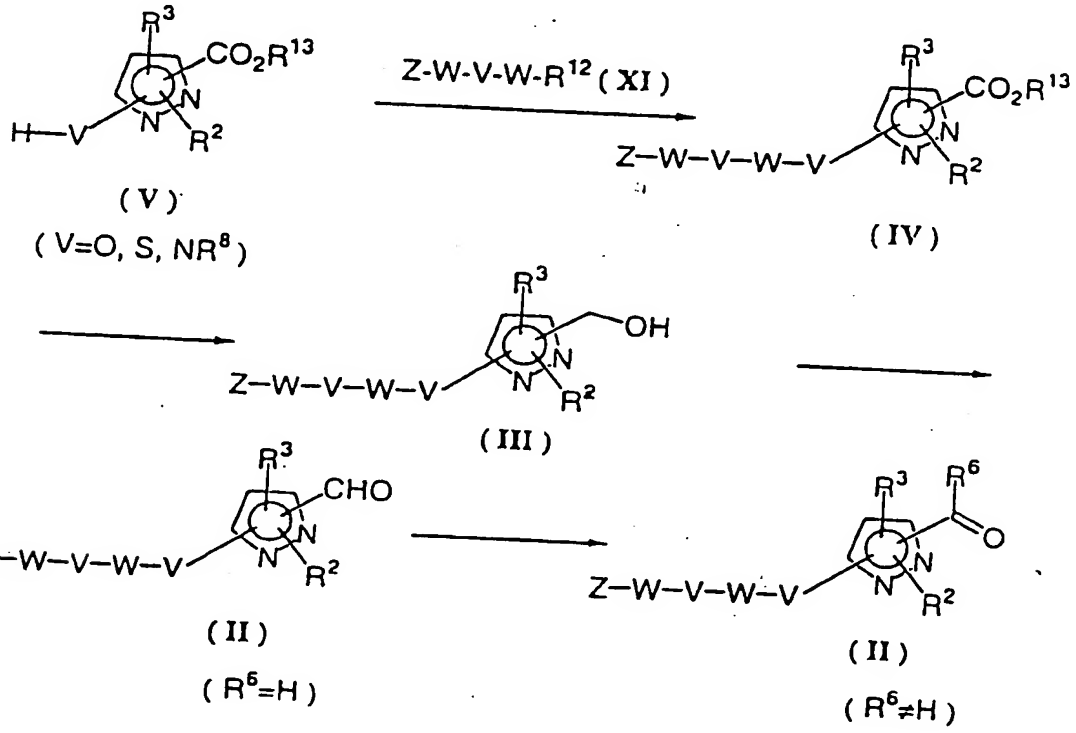
This reaction is conducted usually at a temperature ranging from -20°C to a boiling point of the solvent used, preferably from 20°C to 150°C, for from 0.5 to 30

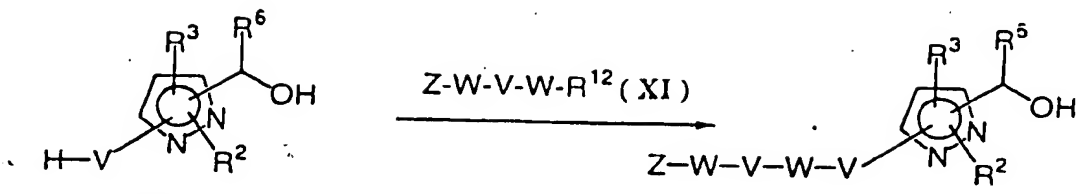
hours.

Among compounds thus obtained, the one having a protecting group on the thiazolidine ring, as represented by the formula (XVIII) can be led to a compound of the formula (I) either in accordance with the method disclosed by T.W. Greene, P.G.M. Wuts in "Protective Groups in Organic Synthesis" (1991) or deprotecting the amide group at the 3-position of the thiazolidine ring by the method described in Process 5.

Now, processes for producing intermediates useful for the preparation of the compounds of the present invention will be described.

Process 7





(XIII)
(V=O, S, NR^8)

(III)

(wherein R^2, R^3, R^6, R^{12}, V, W and Z are as defined above, and R^{13} is a C_1-C_7 alkyl group, or a benzyl group which may be substituted by a methoxy group or an ethoxy group).

A compound of the formula (II) wherein R^6 is hydrogen, can be prepared by using a pyrazole carboxylic acid ester of the formula (V) as a starting material. Namely, a hydroxyl group, a thiol group or an amino group directly bonded to the pyrazole of the compound (V) (VH, V=O, S, NR^8) is subjected to nucleophilic substitution with a compound of the formula (XI) to obtain a compound of the formula (IV). The carboxylic acid ester group of the compound (IV) is reduced to obtain a compound of the formula (III). The compound (III) can be converted to a compound of the formula (II) by oxidizing its hydroxymethyl group.

Among pyrazole carboxylic acid esters of the formula (V), a compound wherein VH is a hydroxyl group can be prepared by methods disclosed in, for example, Chem. Pharm. Bull., vol. 31(4), P1228 (1983) (R^2=H, R^3=H), Can. J. Chem., vol 55(1), p145 (1977) (R^2=H, R^3=Ph), J.

Heterocyclic Chem., vol 30(4), P1097 (1993), Japanese Unexamined Patent Publication No. 185964/1988, Chem. Pharm. Bull., vol. 31(4), P1228 (1983), Chem. Ber., vol. 109(1), P253(1976) and the like (R^2=1-Me, R^3=H), German Laid Open Patent Application No. 2219484 (R^2=1-Me, R^3=Me), German Laid Open Patent Application 2219484 (R^2=1-Me, R^3=Cℓ), Chem. Ber., vol. 109(1), P261 (1976) (R^2=1-Me, R^3=Br), German Laid Open Patent Application 2928136 (R^2=1-Ph, R^3=H), Chem. Ber., vol. 112(5), P1712 (1979) (R^2=1-CH_2Ph, R^3=H), Justus Liebigs Ann. Chem., vol., 757, P100 (1972) (R^2=1-(2-Py), R^3=H), J. Chem. Soc., Perkin Trans. 1, vol.(2), P297 (1974) (R^2=1-(2-benzthiazolyl), R^3=H), J. Chem. Soc., Perkin Trans. 1, vol. (2), P297 (1974) (R^2=1-(2-benzimidazolyl), R^3=H). Further, a compound represented by (R^2=2-Me, R^3=H) can be obtained by hydrolyzing, by a conventional method, a benzoyloxy compound obtained by the method disclosed in Chem. Ber., vol. 111(2), P780 (1978). Likewise, a compound represented by (R^2=2-Et, R^3=H) can be obtained by hydrolyzing, by a conventional method, an acetoxy compound obtained by the method disclosed in Chem. Ber., vol. 107(4), P1318 (1974). Similarly, a compound represented by (R^2=2-Ph, R^3=H) can be obtained by hydrolyzing, by a conventional method, an acetoxy compound obtained by the method disclosed in e.g. Yakugaku Zasshi, vol. 83, P725 (1963).

Further, a compound represented by (R^2=2-Me, R^3=Me)

or (R^2=2-Me, R^3=Br) can also be prepared by subjecting a methoxypyrazole carboxylic acid amide derivative obtained by the method disclosed in European Patent Publication No. 394043 to methyl removal and hydrolysis of the amide group by appropriate conventional methods to obtain a pyrazole carboxylic acid, and esterifying the pyrazole carboxylic acid by means of a conventional method.

Among pyrazole carboxylic acid esters of the formula (V), a compound wherein VH is a thiol group, can be obtained, for example, by preparing a pyrazolesulfonyl halide using a pyrazolesulfonic acid disclosed in e.g. J. Org. Chem., vol. 28(12), P3433 (1963) (V=S, R^2=H, R^3=H) as a starting material and a conventional appropriate halogenating agent such as phosphorus pentachloride, phosphoryl chloride or chorosulfuric acid, and then reducing the pyrazolesulfonyl halide with an appropriate reducing agent such as zinc/hydrochloric acid, zinc amalgam, tin chloride, lithium aluminum hydride or diborane.

Among pyrazole carboxylic acid esters of the formula (V), a compound wherein VH is an amino group can be prepared in accordance with a method disclosed in e.g. Khim.-Farm. Zh., vol. 20(8), P947 (1986) (V=NH, R^2=H, R^3=H), German Laid Open Patent Application No. 2838029, Japanese Unexamined Patent Publication No. 65089/1984, J. Org. Chem., vol. 54(2), P428(1989), Chem. Pharm. Bull., vol. 35(8), P3235 (1987) and the like (V=NH, R^2=1-Me,

R^3=H), Japanese Unexamined Patent Publication No. 20955/1992 (V=NH, R^2=1-Ph, R^3=H).

The step for preparing the compound of the formula (IV) is usually carried out in the same manner under the same condition as described in Process 6.

Further, among compounds of the formula (IV), a compound represented by (-V-Z=NHPh, R^2=H, R^3=H) can be prepared also in accordance with the method disclosed in Collect. Czech. Chem. Commun., vol. 57(3), P656 (1992). A compound represented by (-V-Z=SPh, R^2=1-Ph, R^3=H) can be prepared also by the method disclosed in Chem. Ber., vol. 112(4), P1193 (1979). Likewise, a compound represented by (-V-Z=SPh, R^2=2-Ph, R^3=H) can be prepared also by the method disclosed in Chem. Ber., vol. 112(4), P1206 (1979). Similarly, a compound represented by (-V-Z=SO_2Ph, R^2=H, R^3=Me) can be prepared also by the method disclosed in Bull. Soc. Chim. Fr., vol. 9-10, Pt.2, P2746 (1973).

The step for preparing the compound of the formula (III) is carried out by using a conventional appropriate reducing agent (for example, a metal hydrogen complex compound such as LAH: lithium aluminum hydride, SAH: sodium aluminum hydride, triethoxyaluminum sodium hydride, Red-Aℓ: bis(2-methoxyethoxy)aluminum sodium hydride, SBH: sodium boron hydride or LBH: lithium boron hydride, a metal hydride compound such as DIBAH: diisobutyl aluminum hydride, or catalytic hydrogenation

using CuBaCrO as the catalyst).

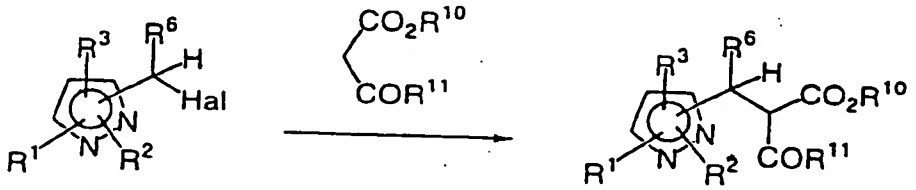
Further, the compound of the formula (III) can be obtained also by subjecting a hydroxymethylpyrazole derivative of the formula (XVIII) wherein R^2, R^3, R^6 and V are as defined above, to nucleophilic substitution with a compound of the formula (XI). The compound of the formula (XIII) can be prepared also by the method disclosed in e.g. J. Heterocycl. Chem., vol. 16(3), P505 (1979) (R^2=H, 1-CH_2Ph, 1-Ph, R^3=H, R^6=H, Me) or Arabian J. Sci. Eng., vol 6(1), P3 (1981) (R^2=1-Me, R^3=H, R^6=H, Me). This step is usually carried out in the same manner under the same condition as described in Process 6.

The step of preparing the compound of the formula (II) can be conducted by using an appropriate oxidizing agent (such as manganese dioxide, PCC: pyridinium chlorochromate, PDC: pyridinium dichromate, DDQ: dichlorodicyanobenzoquinone, chloranil, Swern oxidation: oxalylchloride-dimethylsulfoxide-tertiary amine, and sulfur trioxide-pyridine complex).

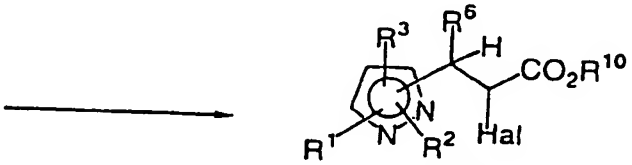
The compound of the formula (II) (R^6=H) obtained by the above-mentioned method, can be further modified into a compound of the formula (II) ($R^6 \neq H$) by alkylating a formyl group with an appropriate alkylating agent by means of a well known method.

This step can be conducted by a method using diazomethane as described in "Tetrahedron Letters, p. 955 (1963)" and "Chem. Ber. vol. 40, p 479 (1907)", a method

using alkyl halide as described in "Synth. Commun., vol. 14(8), p. 743 (1984)" or a method using alkyl lithium as described in "J. Org. Chem., vol. 30, p. 226 (1965)".



(XVI) (XVII)



(VII)

(wherein R^1, R^2, R^3, R^6, R^{10} and Hal are as defined above, and R^{11} represents OR^{10} (R^{10} is as defined above) or C_1-C_3 alkyl such as methyl, ethyl, n-propyl and i-propyl).

A halocarboxylic acid ester of the formula (VII) can be obtained by reacting a halomethylpyrazole of the formula (XVI) with a malonic acid ester or a lower acylacetic acid ester by a known method to form a compound of the formula (XVII), and by halogenating the compound thus formed.

The halomethylpyrazole of the formula (XVI) can be obtained also by halogenating a hydroxymethylpyrazole derivative of the formula (XIII) wherein R^2, R^3, R^6 and V are as defined above, by a conventional method, for example by using e.g. $SOC\ell_2$, $POC\ell_3$, $PC\ell_5$, $HC\ell$, $SnC\ell_4$, HBr, PBr_3, Br_2, $POBr_3$, mecylchloride or tosylchloride.

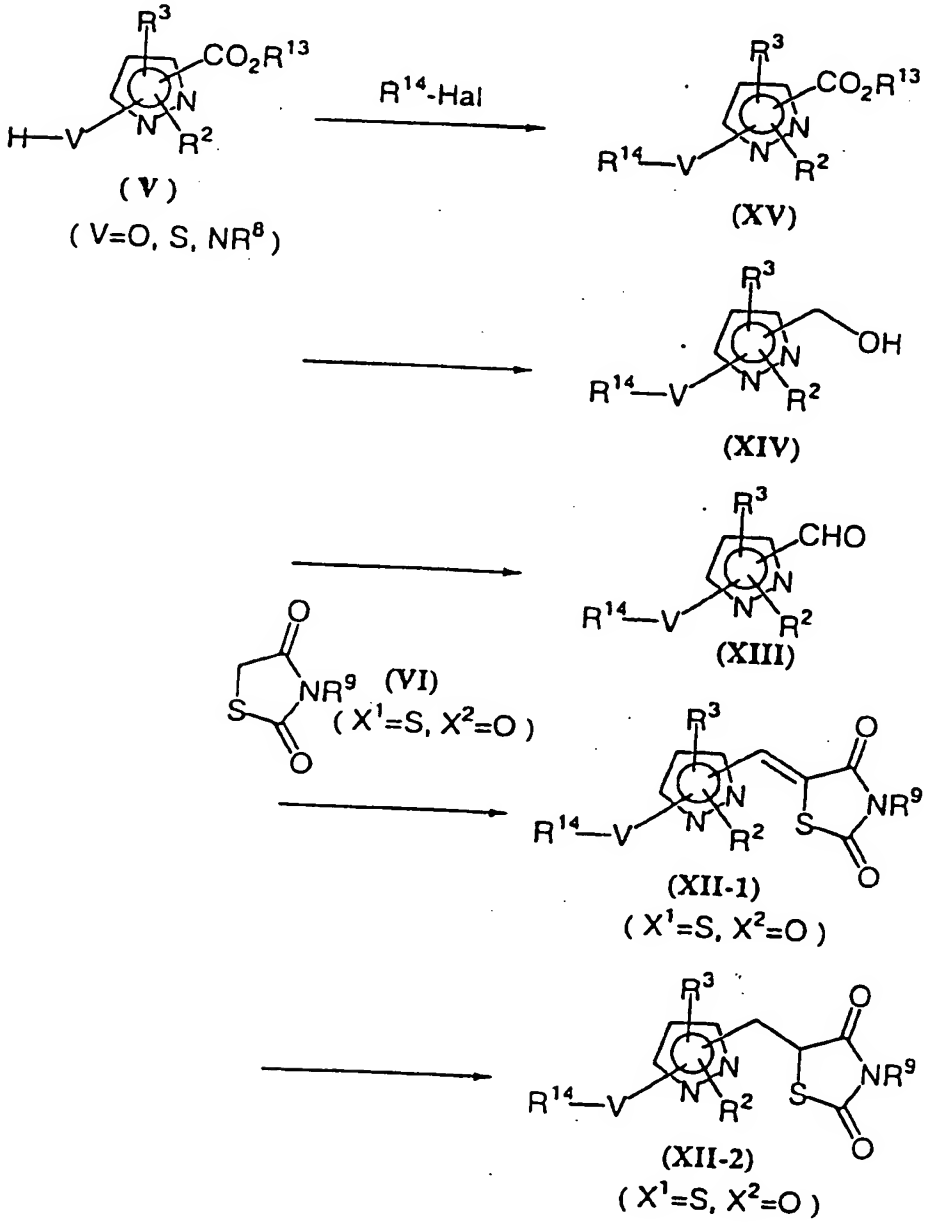
Among the compounds having the formula (XVII), a compound wherein R^{11} is C_1-C_3 alkyl, can be obtained by reacting a halomethylpyrazole of the formula (XVI) with a lower acylacetic acid ester such as methyl acetoacetate and ethyl acetoacetate in the presence of an appropriate base (such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium amide, potassium amide, diisopropyl amide, butyl lithium, metal sodium and potassium carbonate) in accordance with such a method as described in "J. Amer. Chem. Soc., vol. 64, p. 435 (1942)".

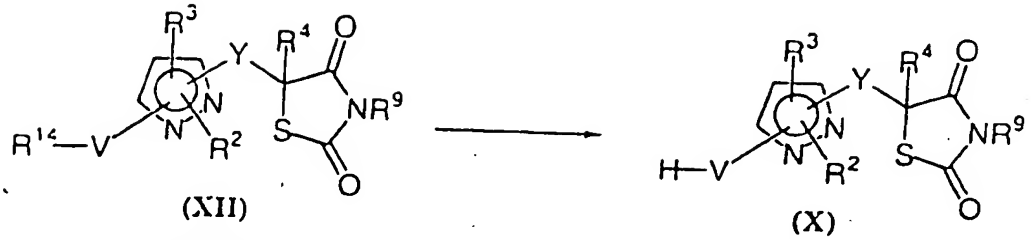
Among the compounds having the formula (VII), a compound wherein R^{11} is OR^{10}, can be obtained by reacting a halomethylpyrazole of the formula (XVI) with a malonic acid ester such as diethyl malonate and di-t-butyl malonate in the presence of an appropriate base as mentioned above, in accordance with such a method as described in "J. Amer. Chem. Soc., vol. 74, p. 831 (1952)" and "Org. Synth. Coll. vol. 3, p. 705 (1955)".

The step of synthesizing a compound of the formula (VII) can be conducted by using an appropriate halogenating agent (such as bromine and N-chlorosuccinimide) in the presence of an appropriate base (such as potassium hydroxide, sodium methoxide and potassium carbonate) in accordance with such a method as described in "J. Amer. Chem. Soc., vol. 71, p. 3107 (1949)" and "Tetrahedron Letters, vol. 28, p. 5505

(1987)".

Also, a compound of the formula (VII) can be obtained by reacting a halomethylpyrazole of the formula (XVI) with a diazoacetic acid ester in the presence of a copper catalyst in accordance with such a method as described in "Zur. Russ. Fiz-Chim., vol. 21, p. 851 (1951)".





(XII)

(XII-1:Y=CR^6R^7 and R^4,R^7=bond
XII-2:Y=CR^6R^7 and R^4,R^7=H)

(X)

(X-1:Y=CR^6R^7 and R^4,R^7=bond
X-2:Y=CR^6R^7 and R^4,R^7=H)

(wherein R^2, R^3, R^9, R^{13}, Hal and V are as defined above, Y is CR^6R^7 (R^6 is hydrogen atom, and R^7 forms a bond together with R^4), and R^{14} is a protecting group for the V-H substituent on the pyrazole ring).

An intermediate of the formula (X) can be prepared also by the following method. Namely, V-H of a compound of the formula (V) is protected by an appropriate protecting group R^{14} to obtain a compound (XV). The ester group of this compound is reduced to obtain a compound (XIV), which is further oxidized to obtain a compound (XIII). This compound (XIII) can be condensed with a compound (VI) (X^1=S, X^2=O, R^9 is a hydrogen atom or a protecting group for amide, e.g. Tr: a trityl group) to obtain a compound (XII-1). The compound (XII-1) can be converted to a compound (XII-2) by reducing its olefin bond portion. By removing the protecting group R^{14} for V-H, the compound (XII-1) or the compound (XII-2) can be converted to a compound (X-1) or a compound (X-2), respectively. The compound (X-1) or the compound (X-2) can be converted to a compound (I-1) or a compound (I-2), respectively, by introducing a -W-V-W-Z group to the V-H

group on the respective pyrazole ring by nucleophilic substitution with a compound (XI).

The compound of the formula (XV) can be obtained by protecting the V-H group of a pyrazole carboxylic acid ester derivative of the formula (V) wherein R^2, R^3, R^{13} and V are as defined above, with an appropriate protecting group R^{14}. As such a protecting group, the one which is stable under the reaction conditions of the subsequent steps, is preferred. For example, a C_1-C_4 alkoxymethyl group (such as MOM: methoxymethyl, MEM: 2-methoxyethoxymethyl, ethoxymethyl, n-propoxymethyl, i-propoxymethyl, n-butoxymethyl, iBM-isobutyloxymethyl, BUM: t-butoxymethyl, POM: pivaloyloxymethyl or SEM: trimethylsilylethoxymethyl, preferably a C_1-C_2 alkoxymethyl), a substituted thiomethyl group (such as MTM: methylthiomethyl), a trialkylsilyl group (such as TMS: trimethylsilyl, TES: triethylsilyl, TIPS: triisopropylsilyl, DEIPS: diethylisopropylsilyl, DMIPS: dimethylisopropylsilyl, DTBMS: di-t-butylmethylsilyl, IPDMS: isopropyldimethylsilyl, TBDMS: t-butyldimethylsilyl or TDS: thexyldimethylsilyl, preferably t-butyldimethylsilyl) or a trialkylarylsilyl group (such as DPMS: diphenylmethylsilyl, TBDPS: t-butyldiphenylsilyl, TBMPS: t-butyldimethoxyphenylsilyl, or TPS: triphenylsilyl), may be mentioned. More preferably, an alkoxyalkyl group such as MOM: a methoxymethyl group, or MEM: a methoxyethoxymethyl group,

or a substituted silyl group such as TBDMS: a t-butyldimethylsilyl group, may, for example, be mentioned. Particularly preferred is a methoxymethyl group.

Such a reaction can be conducted in accordance with the method disclosed e.g. by T.W. Greene, P.G.M. Wuts in "Protective Groups in Organic Synthesis" (1991). In a case where R^{14} is a methoxymethyl group, the reaction can be conducted at room temperature by using e.g. methoxymethyl chloride in the presence of diisopropylethylamine.

The compound (XV) thus obtained is subjected to reduction of the ester group in the same method as in the step for producing a compound (II) from a compound (IV) as disclosed in Process 7, to obtain a compound (XIV), which is further oxidized to obtain a compound (XIII).

The step for preparing the compound of the formula (XII-1) is a step of dehydrating and condensing the compound (XIII) and a thiazolidine derivative of the formula (VI) wherein X^1 is S, X^2 is O, and R^9 is a hydrogen atom or a protecting group for amide (such as Tr: trityl) under an appropriate condition, and such dehydration condensation can be carried out in the same manner under the same condition as described in Process 1.

The compound (XII-1) thus obtained can be converted to a compound (XII-2) by reducing the olefin bond portion under an appropriate reducing condition. Such a method

will be described in detail in the paragraph relating to mutual conversion of a partial structure of the compound (I).

The compound (XII) can be converted to a compound (X) by removing the protecting group R^{14} for the V-H group. Such a reaction can be conducted in accordance with e.g. the method disclosed by T.W. Greene, P.G.M. Wuts in "Protective Groups in Organic Synthesis" (1991). In a case where R^{14} is an alkoxyalkyl group such as MOM: a methoxymethyl group or MEM: a methoxyethoxymethyl group, the reaction can be conducted within a temperature range of from room temperature to the boiling point of the solvent in methanol, ethanol or tetrahydrofuran by means of an inorganic acid such as hydrochloric acid or sulfuric acid, or an organic acid such as trifluoroacetic acid, or within a temperature range of from room temperature to -78°C in methylene chloride by means of e.g. zinc bromide, dimethylborane bromide, diisopropylthioborane bromide or diphenylborane bromide. Further, in a case where R^{14} is substituted silyl group such as TBDMS: a t-butyldimethylsilyl group, the reaction can be conducted within a temperature range of from -78°C to the boiling point of the solvent used, in tetrahydrofuran, dioxane or acetonitrile by means of tetrabutylammonium fluoride, potassium fluoride, a pyridine/hydrogen fluoride complex, or a trifluoroborane/ether complex.

In a case where a substituent is to be introduced by nucleophilic substitution to the V-H group on the pyrazole ring in the compound of the formula (X), it is preferred to protect the acidic hydrogen atom at the thiazolidine ring with an appropriate protecting group. In such a case, in the process for obtaining the compound (XII-1) from the compound (XIII), it is possible to employ a compound (VI) wherein hydrogen for R^9 is protected by an appropriate substituent (such as Tr: trityl), as the starting material. Further, in the compound (XII-1), the compound (XII-2) and the compound (X), the substituent R^9 on the thiazolidine ring is a hydrogen atom, such acidic proton may be protected by means of an appropriate protecting group. In such a case, the protecting group is preferably the one which is stable even in the nucleophilic substitution reaction of the V-H group as described in Process 6. For example, a C_1-C_4 alkoxymethyl group (such as MOM: methoxymethyl), a substituted silyl group (such as TBDMS: t-butyldimethylsilyl), an arylmethyl group (such as Tr: trityl, DMTr: Di(4-methoxyphenyl)phenylmethyl, or DAM: di(4-methoxyphenyl)methyl), an aryloxycarbonyl group (such as Z: benzyloxycarbonyl), or a C_1-C_4 alkoxycarbonyl group (such as BOC: t-butoxycarbonyl) may be mentioned. Preferred may, for example, be trityl or benzyloxycarbonyl.

Such a protecting group may be introduced or removed

in accordance with e.g. the methods disclosed by T.W. Greene, P.G.M. Wuts in "Protective Groups in Organic Synthesis" (1991). For example, the reactions may be conducted under such conditions as follows: MOM: methoxymethyl (introduction: methoxymethyl chloride; removal: hydrochloric acid or trifluoroacetic acid), TBDMS: t-butyldimethylsilyl (introduction: t-butyldimethylsilyl chloride; removal: tetrabutylammonium fluoride), Tr: trityl (introduction: trityl chloride, triethylamine; removal: hydrochloric acid or trifluoroacetic acid), Z: benzyloxycarbonyl (introduction: benzyloxycarbonyl chloride; removal: catalytic hydrogenation in the presence of a palladium carbon catalyst), and BOC: t-butoxycarbonyl (introduction: t-butoxycarbonyl anhydride; removal: catalytic hydrogenation in the presence of a palladium/carbon catalyst).

Now, with respect to the compound of the formula (I) thus obtained, a method for mutual conversion of its partial structure, will be described.

(I-1)
(R^4, R^7=bond)

(I-2)
(R^4=H, R^7=H)

(wherein R^1, R^2, R^3, R^6, R^9, X^1 and X^2 are as defined

above).

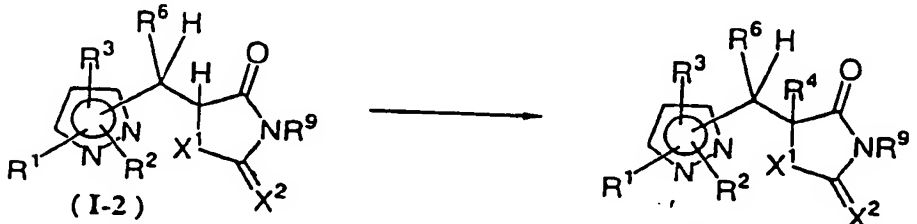
A compound of the formula (I-1) (wherein R^4 and R^7 are bonded together) obtained by the above method can be modified into a compound of the formula (I-2) (R^4, R^7=H) by appropriately reducing a double bond between a pyrazole ring and a thiazolidine or oxazolidine ring (for example by catalytic hydrogenation in the presence of an appropriate catalyst, by using an appropriate metal-hydrogen complex compound, or by using magnesium or sodium amalgam in a lower alcohol such as methanol).

The catalytic hydrogenation is conducted usually in alcohols, cellosolves, aprotic polar organic solvents, ethers, alkoxyalkanes, lower aliphatic acid esters or lower aliphatic acids, and particularly methanol, ethanol, methoxyethanol, dimethylformamide, tetrahydrofuran, dioxane, dimethoxyethane, ethyl acetate or acetic acid is preferably used alone or in a mixture. Examples of the catalyst used include palladium black, palladium carbon and platinum oxide. This reaction can proceed at normal temperature under normal pressure, but it is preferable to conduct the reaction at an elevated temperature under a increased pressure depending on the reactivity of the aimed reaction.

The reduction by a metal-hydrogen complex compound is conducted by using sodium borohydride, potassium borohydride, lithium borohydride, tetramethyl ammonium borohydride or zinc borohydride in an aprotic polar

organic solvent at a temperature ranging from 0°C to 150°C, preferably from 0°C to 30°C. In this reduction, undesired side-reaction can be inhibited by using a Co reagent such as $CoC\ell_2$, $CoC\ell_3$ or $Co(OAc)_2$ in the presence of a ligand such as dimethyl glyoxime, 2,2'-bipyridyl or 1,10-phenanthroline (see WO93/13095).

In the case of using amalgam, the reduction can be conducted usually in an alcohol, preferably in methanol or ethanol, within a temperature range of from -20°C to the boiling point of the solvent, preferably from 0°C to 50°C. Further, the reduction method by magnesium/methanol as disclosed in J. Org. Chem., vol. 40, P127 (1975), may also be employed.



(I-2)
(R^4=H, R^7=H)

(I-2)
($R^4 \neq$H, R^7=H)

(wherein R^1, R^2, R^3, R^4, R^6, R^9, X^1 and X^2 are as defined above).

A compound of the formula (I-2) (R^4, R^7=H) can be modified into a compound of the formula (I-2) ($R^4 \neq$H, R^7=H) by alkylating hydrogen at the 5-position of thiazolidine or oxazolidine with an appropriate alkylating agent (such as alkyl halide including methyl iodide or ethyl iodide, alkyl sulfate including dimethyl

sulfate or diethyl sulfate, and aliphatic or aromatic sulfonic acid esters including methyl tosylate or methyl mesylate) in accordance with a well known method.

This reaction is conducted usually in an appropriate organic solvent in the presence of base. Examples of the solvent thus used include aprotic polar organic solvents, ethers, alkoxyalkanes and the like, and among them, tetrahydrofuran and dimethoxyethane are particularly preferable. Examples of the base include alkali metal amides (such as lithium diisopropylamide (LDA) and potassium amide) and aliphatic or aromatic lithium compounds (such as n-butyl lithium, t-butyl lithium and phenyl lithium). These materials are selected appropriately depending on the reactivity of the aimed reaction.

This reaction is conducted usually at a temperature ranging from -20°C to 100°C, preferably from -10°C to 30°C, for from 0.1 to 10 hours.

(I-2e)
(X^1=S, X^2=NH)

(I-2a)
(X^1=S, X^2=O)

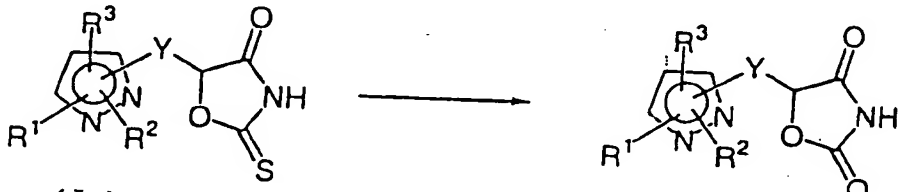
(wherein R^1, R^2, R^3 and R^6 are as defined above).

A compound of the formula (I-2e) (X^1=S, X^2=NH) can be modified into a compound of the formula (I-2a) (X^1=S,

X^2=O) by hydrolyzing an imino group at the 2-position of the thiazolidine in accordance with a well known method.

This reaction is conducted usually in an appropriate organic solvent in the presence of water or acid. Examples of the solvent thus used include alcohols, cellosolves, aprotic polar organic solvents, ethers, alkoxyalkanes, and the like, and particularly methanol, ethanol, methoxyethanol, sulfolane, dioxane and dimethoxyethane are preferably used. Examples of the acid thus used include inorganic acids (such as hydrochloric acid, sulfuric acid and hydrobromic acid). These materials are selected appropriately depending on the reactivity of the aimed reaction.

This reaction is conducted usually at a temperature of from 50°C to a boiling point of a solvent used, preferably from 80°C to 150°C, for from 0.5 to 30 hours.



(Ic)
(X^1=O, X^2=S)

(Id)
(X^1=O, X^2=O)

A compound of the formula (Ic) (X^1=O, X^2=S) can be modified into a compound of the formula (Id) (X^1=O, X^2=O) by oxidizing a thioxo group at the 2-position of thiazolidine in accordance with a well known method.

This reaction is conducted by using an appropriate

oxidizing agent (such as hydrogen peroxide, an organic peroxide including peracetic acid, perbenzoic acid, methachloroperbenzoic acid, monopermaleic acid, monoperphthalic acid and the like, mercury ion, bromine, chlorine and meta-periodic acid) generally in water or in a solvent such as aprotic polar organic solvents (e.g. dimethylformamide, dimethylsulfoxide, dimethylacetamide, tetramethylurea, sulfolane and N,N-dimethylimidazolidinone), ethers (e.g. tetrahydrofuran and dioxane), and alkoxyalkanes (e.g. dimethoxyethane and diethoxyethane). These materials are selected appropriately depending on the reactivity of the aimed reaction, and are used respectively alone or in combination.

This reaction is conducted generally at a temperature ranging from 0°C to a boiling point of a solvent used, preferably from 20°C to 100°C, for from 0.5 to 30 hours.

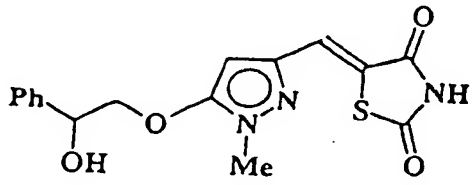
The above-mentioned compounds (II), (III), (IV), (VII), (VIII), (IX), (X), (XII), (XIII), (XIV), (XV), (XVI) and (XVII) are novel compounds, and are useful as intermediate products for preparing the compound of the formula (I) of the present invention.

BEST MODE FOR CARRYING OUT THE INVENTION

Now, the present invention will be described in further detail with reference to Examples for preparation of the compounds of the present invention, Pharmacological Test Examples and Formulation Examples. However, it should be understood that the present invention is by no means restricted by such specific Examples.

EXAMPLE 1

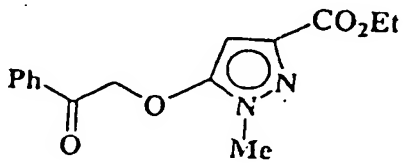
Preparation of 5-((5-(2-hydroxy-2-phenylethoxy)-1-methyl-3-pyrazolyl)methylidene)thiazolidin-2,4-dione (Compound No. I-1a-1)



(I-1a-1)

Step 1

Ethyl 1-methyl-5-phenacyloxy-3-pyrazolecarboxylate (Compound No. IV-1)



(IV-1)

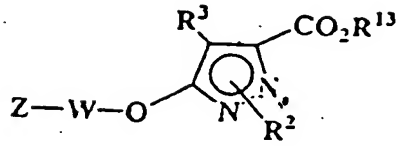
171 mg (1.00 mmol) of ethyl 5-hydroxy-1-methyl-3-pyrazolecarboxylate (Compound No. V-1) (prepared in accordance with a method disclosed in Japanese Unexamined Patent Publication No. 185964/1988) and 170 mg (1.10

mmol) of phenacyl chloride (TCI) were dissolved in dimethylformamide dehydrated with molecular sieves. To this solution, 144 mg of anhydrous potassium carbonate was added, and the mixture was stirred at room temperature overnight. To this reaction solution, 5 mℓ of a saturated sodium chloride aqueous solution was added, and the mixture was extracted with 45 mℓ of chloroform. The organic layer was washed with a saturated sodium chloride aqueous solution and then dried over anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was distilled off under reduced pressure. The residue thereby obtained was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 2/1) to obtain 285 mg (98.6%) of the desired substance (Compound No. IV-1) as colorless powder.

MS(FAB) m/e: 289$(M+H)^+$

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.35(3H, t), 3.79(3H, s), 4.33(2H, q), 5.31(2H, s), 5.98(1H, s), 7.40-7.65(3H, m), 7.8-8.0(2H, m)

In the same manner as above, Compounds Nos. IV-2 to IV-13 were prepared by using Compound No. V-1, ethyl 1-t-butyl-5-hydroxy-3-pyrazolecarboxylate (Compound No. V-2) and ethyl 5-hydroxy-1-phenyl-3-pyrazolecarboxylate (Compound No. V-3) as starting materials. (R^2, R^3, R^{13}, W and Z in the Table correspond to the substituents of Compound No. IV.)



(IV)

R^1=O-W-Z

Starting material	Compound No.	R^2	R^3	R^{13}	Z-W
V-1	IV-2	1-Me	H	Et	$PhCH_2CH_2$
V-2	IV-3	1-t-Bu	H	Et	$PhCOCH_2$
V-3	IV-4	1-Ph	H	Et	$PhCOCH_2$
V-1	IV-5	1-Me	H	Et	5-Me-2-Ph-4-oxazolyl-$COCH_2$
V-2	IV-6	1-t-Bu	H	Et	5-Me-2-Ph-4-oxazolyl-$COCH_2$
V-3	IV-7	1-Ph	H	Et	5-Me-2-Ph-4-oxazolyl-$COCH_2$
V-1	IV-8	1-Me	H	Et	3-Me-2-benzo[b]thiophenyl-$COCH_2$
V-1	IV-9	1-Me	H	Et	2-benzo[b]furanyl-$COCH_2$
V-1	IV-10	1-Me	H	Et	5-Me-1-Ph-4-pyrazolyl-$COCH_2$
V-1	IV-11	1-Me	H	Et	3-Br-1-Me-2-indolyl-$COCH_2$
V-1	IV-12	1-Me	H	Et	3-indolyl-CH_2CH_2
V-1	IV-13	1-Me	H	Et	3-Ph-5-isoxazolyl-$COCH_2$

Compound No.	Properties	mp (°C)	MS (m/e)
IV-2	Colorless powder		274(M)$^+$EI
IV-3	Brown powder		331(M+H)$^+$FAB
IV-4	Brown oil		351(M+H)$^+$FAB
IV-5	Pale yellow powder	181.8-183.2	370(M+H)$^+$FAB
IV-6	Pale brown powder		411(M)$^+$EI
IV-7	Pale brown powder		431(M)$^+$EI
IV-8	Pale brown powder		358(M)$^+$EI
IV-9	Pale yellow powder		328(M)$^+$EI
IV-10	Colorless powder		368(M)$^+$EI
IV-11	Colorless crystals		419(M)$^+$EI
IV-12	Purple powder		313(M)$^+$EI
IV-13	Pale brown powder		356(M+H)$^+$FAB

IV-2

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.35(3H, t), 3.07(2H, t), 3.66(3H, s), 4.29(2H, t), 4.3(2H, q), 6.07(1H, s), 7.25(5H, s)

IV-3

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.34(3H, t), 1.68(9H, s), 4.30(2H, q), 5.32(2H, s), 6.02(1H, s), 7.3-7.6(3H, m), 7.8-8.0(2H, m)

IV-4

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.35(3H, t), 4.35(2H, q), 5.38(2H, s), 6.12(1H, s), 7.3-7.6(6H, m), 7.7-7.9(4H, m)

IV-5

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.40(3H, t), 2.73(3H, s), 3.86(3H, s), 4.35(2H, q), 5.36(2H, s), 6.06(1H, s), 7.3-7.5(3H, m), 7.8-8.1(2H, m)

IV-6

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.35(3H, t), 1.70(9H, s), 2.72(3H, s), 4.32(2H, q), 5.33(2H, s), 6.07(1H, s), 7.4-8.1(5H, m)

IV-7

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.37(3H, t), 2.72(3H, s), 4.37(2H, q), 5.42(2H, s), 6.18(1H, s), 7.3-8.1(10H, m)

IV-8

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.35(3H, t), 2.79(3H, s), 3.85(3H, s), 4.35(2H, q), 5.18(2H, s), 6.07(1H, s), 7.42-7.55(2H, m), 7.78-7.98(2H, m)

IV-9

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.40(3H, t), 3.88(3H, s), 4.39(2H, q), 5.38(2H, s), 6.12(1H, s), 7.32-7.88(5H, m)

IV-10

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.37(3H, t), 2.61(3H, s), 3.85(3H, s), 4.36(2H, q), 5.11(2H, s), 6.07(1H, s), 7.50(5H, s), 8.09(1H, s)

IV-11

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.36(3H, t), 3.84(3H, s), 4.01(3H, s), 4.37(2H, q), 5.51(2H, s), 6.07(1H, s), 7.11-7.77(4H, m)

IV-12

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.35(3H, t), 3.26(2H, t),

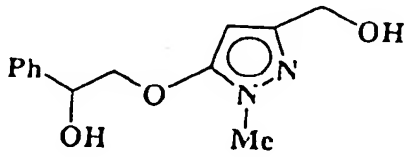
3.66(3H, s), 4.31(2H, t), 4.37(2H, q), 6.03(1H, s), 7.05-8.1(6H, m)

IV-13

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.37(3H, t), 3.87(3H, s), 4.37(2H, q), 5.35(2H, s), 6.07(1H, s), 7.35-7.92(6H, m)

Step 2

3-Hydroxymethyl-5-(2-hydroxy-2-phenylethoxy)-1-methylpyrazole (Compound No. III-1)



(III-1)

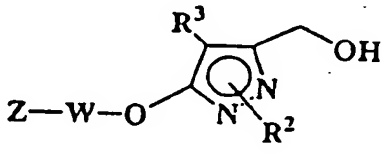
A suspension of 897 mg (23.6 mmol) of lithium aluminum hydride in 50 mℓ of tetrahydrofuran dehydrated by molecular sieves, was cooled to 0°C in a nitrogen atmosphere, and a solution of 4.53 g (15.7 mmol) of Compound IV-1 in 100 mℓ of tetrahydrofuran dehydrated by molecular sieves, was gradually dropwise added thereto. After the dropwise addition, ice bath was taken off, and the mixture was stirred at room temperature for 5.5 hours. To this reaction solution, hydrous magnesium sulfate was added to terminate the reaction. Then, the inorganic salt was removed by filtration with celite and thoroughly washed with tetrahydrofuran. The solvent in the filtrate was distilled off under reduced pressure. The residue thereby obtained was subjected to silica gel column chromatography (eluent: 6% methanol/chloroform) to

obtain 4.44 g (quantitative) of the desired substance (Compound No. III-1) as pale yellow solid.

MS(EI) m/e: 248$(M)^+$

60 MHz ^{1}H-NMR($CDCl_3$)δ: 3.2-4.2(2H, br), 3.44(3H, s), 4.06(2H, d), 4.41(2H, s), 5.02(1H, t), 5.44(1H, s), 7.30(5H, s)

In the same manner, Compounds Nos. III-2 to III-13 were prepared by using Compounds Nos. IV-2 to IV-13 as starting materials. (R^2, R^3, W and Z in the Table correspond to the substituents of Compound No. III.)



(III)
R^1=O-W-Z

Starting material	Compound No.	R^2	R^3	Z-W
IV-2	III-2	1-Me	H	$PhCH_2CH_2$
IV-3	III-3	1-t-Bu	H	$PhCH(OH)CH_2$
IV-4	III-4	1-Ph	H	$PhCH(OH)CH_2$
IV-5	III-5	1-Me	H	5-Me-2-Ph-4-oxazolyl-$CH(OH)CH_2$
IV-6	III-6	1-t-Bu	H	5-Me-2-Ph-4-oxazolyl-$CH(OH)CH_2$
IV-7	III-7	1-Ph	H	5-Me-2-Ph-4-oxazolyl-$CH(OH)CH_2$

IV-8	III-8	1-Me	H	3-Me-2-benzo[b]thiophenyl-CH(OH)CH_2
IV-9	III-9	1-Me	H	2-benzo[b]furanyl-CH(OH)CH_2
IV-10	III-10	1-Me	H	5-Me-1-Ph-4-pyrazolyl-CH(OH)CH_2
IV-11	III-11	1-Me	H	3-Br-1-Me-2-indolyl-CH(OH)CH_2
IV-12	III-12	1-Me	H	3-indolyl-CH_2CH_2
IV-13	III-13	1-Me	H	3-Ph-5-isoxazolyl-CH(OH)CH_2

Compound No.	Properties	mp (°C)	MS (m/e)
III-2	Colorless powder		232(M)$^+$EI
III-3	Brown oil		290(M)$^+$EI
III-4	Pale yellow powder		310(M)$^+$EI
III-5	Brown oil		329(M)$^+$EI
III-6	Red amorphous		371(M)$^+$EI
III-7	Brown amorphous		391(M)$^+$EI
III-8	Pale brown powder		318(M)$^+$EI
III-9	Reddish brown amorphous		288(M)$^+$EI
III-10	Pale yellow amorphous		329(M+H)$^+$FAB
III-11	Orange amorphous		380(M+H)$^+$FAB
III-12	Brown amorphous		271(M)$^+$EI
III-13	Reddish brown amorphous		315(M)$^+$EI

Compound No. (III-2)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 3.0(1H, br s), 3.03(2H, t), 3.48(3H, s), 4.16(2H, t), 4.48(2H, br s), 5.46(1H, s), 7.16(5H, s)

Compound No. (III-3)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.46(9H, s), 2.9(2H, br), 4.08(2H, d), 4.43(2H, s), 5.04(1H, t), 5.50(1H, s), 7.31(5H, s)

Compound No. (III-4)

60 MHz ^{1}H-NMR($CDCl_3$) δ: 2.2(2H, br), 4.19(2H, d), 4.60(2H, s), 5.1(1H, t), 5.66(1H, s), 7.2-7.5(10H, m)

Compound No. (III-5)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 2.42(3H, s), 2.6(2H, br s), 3.57(3H, s), 4.26(2H, m), 4.49(2H, s), 5.0(1H, m), 5.54(1H, s), 7.3-8.1(5H, m)

Compound No. (III-6)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.48(9H, s), 2.40(3H, s), 2.4(2H, br s), 4.28(2H, d), 4.51(2H, s), 5.03(1H, t), 5.57(1H, s), 7.2-8.0(5H, m)

Compound No. (III-7)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 2.25(3H, s), 4.33(2H, d), 4.55(2H, s), 4.98(1H, t), 5.70(1H, s), 7.2-8.0(10H, m)

Compound No. (III-8)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 2.42(3H, s), 3.3(2H, br), 3.59(3H, s), 4.26(2H, d), 4.46(2H, s), 5.53(1H, t), 5.58(1H, s), 7.35-7.92(4H, m)

Compound No. (III-9)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 3.53(3H, s), 4.4(2H, s), 4.40(2H, br), 4.43(2H, d), 5.22(1H, t), 5.68(1H, s), 6.79(1H, s), 7.12-7.57(4H, m)

Compound No. (III-10)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 2.31(3H, s), 3.55(3H, s), 3.7(2H, br), 4.19(2H, d), 4.48(2H, s), 5.05(1H, m), 5.55(1H, s), 7.40(5H, s), 7.59(1H, s)

Compound No. (III-11)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 2.96(3H, s), 3.50(2H, s), 3.88(3H, s), 4.35(2H, d), 4.46(2H, s), 5.53(1H, s), 5.6(1H, m), 7.00-7.57(4H, m)

Compound No. (III-12)

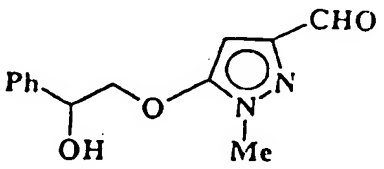
60 MHz ^{1}H-NMR($CDCl_3$)δ: 2.53(1H, s), 3.22(2H, t), 3.53(3H, s), 4.27(2H, t), 4.51(2H, s), 5.49(1H, s), 7.05-8.29(6H, m)

Compound No. (III-13)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 3.49(3H, s), 3.6(2H, br), 4.32(2H, d), 4.49(2H, s), 5.23(1H, t), 5.56(1H, s), 6.62(1H, s), 7.25-7.86(5H, m)

Step 3

5-(2-Hydroxy-2-phenylethoxy)-1-methylpyrazole-3-carbaldehyde (Compound No. II-1)



(II-1)

Preparation of Compound No. 2 by oxidation of manganese

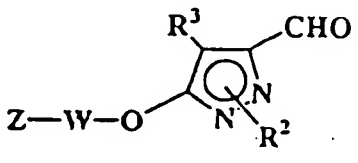
dioxide

2.72 g (11.0 mmol) of Compound No. III-1 was dissolved in 108 mℓ of chloroform and 2 mℓ of methanol. To this solution, 5.23 g of active manganese dioxide was added, and the mixture was stirred at room temperature for 8 hours. The oxidant residue was removed by filtration with celite. Then, the solvent in the obtained filtrate was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 5/2) to obtain 1.53 g (56.6%) of the desired substance (Compound No. II-1) as colorless oil.

MS(EI) m/e: 246$(M)^+$

60 MHz ^{1}H-NMR($CDCl_3$)δ: 2.80(1H, brs), 3.69(3H, s), 4.13(2H, d), 5.07(1H, t), 5.95(1H, s), 7.34(5H, s), 9.62(1H, s)

In the same manner, Compounds Nos. II-2 to II-6 were prepared by using Compounds Nos. III-2 to III-5 as starting materials. Compounds Nos. II-3 and II-4 were simultaneously formed by the reaction of Compound No. III-3 as the starting material. (R^2, R^3, W and Z in the Table correspond to the substituents of Compound No. II.)



(II)

R^1=O-W-Z

R^6=H

Starting material	Compound No.	R^2	R^3	Z-W
III-2	II-2	1-Me	H	$PhCH_2CH_2$
III-3	II-3	1-t-Bu	H	$PhCH(OH)CH_2$
III-3	II-4	1-t-Bu	H	$PhCOCH_2$
III-4	II-5	1-Ph	H	$PhCH(OH)CH_2$
III-5	II-6	1-Me	H	5-Me-2-Ph-4-oxazolyl-$CH(OH)CH_2$

Compound No.	Properties	mp (°C)	MS (m/e)
II-2	Colorless oil		230(M)$^+$EI
II-3	Pale yellow oil		288(M)$^+$EI
II-4	Colorless needles		244(M)$^+$EI
II-5	Yellow oil		308(M)$^+$EI
II-6	Brown oil		327(M)$^+$EI

Compound No. (II-2)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 3.08(2H, t), 3.67(3H, s), 4.25(2H, t), 5.95(1H, s), 7.21(5H, s), 9.67(1H, s)

Compound No. (II-3)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.56(9H, s), 2.69(1H, br), 4.16(2H, d), 5.10(1H, t), 6.01(1H, s), 7.32(5H, s), 9.65(1H, s)

Compound No. (II-4)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 3.84(3H, s), 5.34(2H, s), 5.96(1H, s), 7.4-7.9(5H, m), 9.70(1H, s)

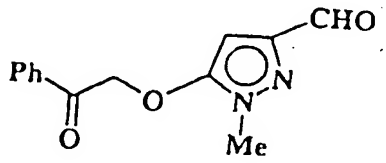
Compound No. (II-5)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 2.63(1H, br), 4.19(2H, d), 5.05(1H, t), 6.11(1H, s), 7.2-7.6(10H, m), 9.77(1H, s)

Compound No. (II-6)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 2.36(3H, s), 3.6(1H, br s), 3.65(3H, s), 4.3(2H, m), 5.02(1H, t), 6.01(1H, s), 7.2-8.0(5H, m), 9.63(1H, s)

1-Methyl-5-phenacyloxypyrazole-3-carbaldehyde (Compound No. II-7)



(II-7)

Preparation of Compound No. II by Swern oxidation

A solution of 175 $\mu\ell$ (2.01 mmol) of oxalyl chloride in 2.5 mℓ of dichloromethane dehydrated by molecular sieves was cooled to -78°C in a nitrogen atmosphere, and a solution of 353 mg (4.98 mmol) of dimethylsulfoxide dehydrated by molecular sieves in 1.5 mℓ of dichloromethane dehydrated by molecular sieves, was dropwise added thereto, and the mixture was stirred at -78°C for 30 minutes. To this solution, a solution of 124 mg (0.500 mmol) of Compound No. III-1 in 3.0 mℓ of dichloromethane dehydrated by molecular sieves, was gradually dropwise added, and then the mixture was

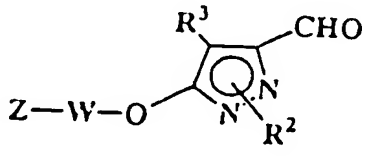
stirred at -78°C for one hour. To this reaction solution, 1.4 mℓ of triethylamine dehydrated by molecular sieves, was dropwise added. Then, the temperature was raised to room temperature, and 5 mℓ of water was added thereto. The mixture was extracted with 45 mℓ of chloroform. The organic layer was dried over anhydrous sodium sulfate, and then the drying agent was filtered off. Then, the solvent in the filtrate was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 1/1) to obtain 101 mg (82.4%) of the desired substance (Compound No. II-7) as colorless needles.

mp 140-141°C

MS(EI) m/e: 244$(M)^+$

60 MHz ^{1}H-NMR($CDCl_3$)δ: 3.84(3H, s), 5.34(2H, s), 5.96(1H, s), 7.4-7.9(5H, m), 9.70(1H, s)

In the same manner, Compounds Nos. II-8 to II-14 were prepared by using Compounds Nos. III-5 to III-11 as starting materials. (R^2, R^3, W and Z in the Table correspond to the substituents of Compound No. II.)



(II)

R^1=O-W-Z

R^6=H

Starting material	Compound No.	R^2	R^3	Z-W
III-5	II-8	1-Me	H	5-Me-2-Ph-4-oxazolyl-$COCH_2$
III-6	II-9	1-t-Bu	H	5-Me-2-Ph-4-oxazolyl-$COCH_2$
III-7	II-10	1-Ph	H	5-Me-2-Ph-4-oxazolyl-$COCH_2$
III-8	II-11	1-Me	H	3-Me-2-benzo[b]thiophenyl-$COCH_2$
III-9	II-12	1-Me	H	2-benzo[b]furanyl-$COCH_2$
III-10	II-13	1-Me	H	5-Me-1-Ph-4-pyrazolyl-$COCH_2$
III-11	II-14	1-Me	H	3-Br-1-Me-2-indolyl-$COCH_2$

Compound No.	Properties	mp (°C)	MS (m/e)
II-8	Pale yellow powder		325(M)$^+$EI
II-9	Pale brown powder	158-160	367(M)$^+$EI
II-10	Pale brown powder	125-128	387(M)$^+$EI
II-11	Pale yellow powder		314(M)$^+$EI
II-12	Orange powder		284(M)$^+$EI
II-13	Colorless powder		324(M)$^+$EI
II-14	Pale brown powder		375(M)$^+$EI

Compound No. (II-8)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 2.69(3H, s), 3.86(3H, s), 5.37(2H, s), 5.99(1H, s), 7.39-7.53(3H, m), 7.90-8.09(2H, m), 9.73(1H, s)

Compound No. (II-9)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.74(9H, s), 2.72(3H, s), 5.40(2H, s), 6.09(1H, s), 7.4-7.6(3H, m), 7.9-8.1(2H, m), 9.77(1H, s)

Compound No. (II-10)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 2.67(3H, s), 5.43(2H, s), 6.13(1H, s), 7.3-8.1(10H, m), 9.86(1H, s)

Compound No. (II-11)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 2.79(3H, s), 3.90(3H, s), 5.18(2H, s), 6.02(1H, s), 7.42-8.10(4H, m), 9.72(1H, s)

Compound No. (II-12)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 3.89(3H, s), 5.38(2H, s), 6.06(1H, s), 7.28-7.84(5H, m), 9.78(1H, s)

Compound No. (II-13)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 2.59(3H, s), 3.89(3H, s), 5.12(2H, s), 6.01(1H, s), 7.50(5H, s), 8.07(1H, s), 9.79(1H, s)

Compound No. (II-14)

60 MHz ^{1}H-NMR($CDCl_3$)δ: 3.87(3H, s), 4.00(3H, s), 5.53(2H, s), 6.03(1H, s), 7.40-7.76(4H, m), 9.75(1H, s)

Preparation of Compound No. II by PCC oxidation

To a suspension of 1.041 g (4.828 mmol) of pyridinium chlorochromate, 401 mg (4.89 mmol) of sodium acetate, 0.50 g of pulverized molecular sieves 4A and 1.01 g of

celite in 30 mℓ of dichloromethane dehydrated by molecular sieves, a solution of 210 mg (0.846 mmol) of Compound III-1 in 10 mℓ of dichloromethane dehydrated by molecular sieves, was dropwise added at 0°C, and the mixture was stirred at 0°C for 90 minutes and then at room temperature for 140 minutes. The inorganic salt was filtered off. Then, the solvent was distilled off under reduced pressure. The residue thereby obtained was subjected to silica gel column chromatography (eluent: 4% methanol/chloroform) to obtain 86 mg (41.5%) of the desired substance (Compound No. II-7) as colorless needles.

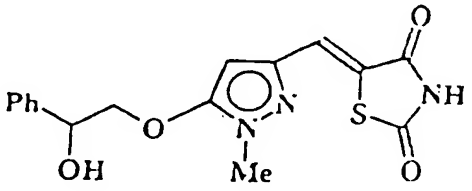
Preparation of Compound No. II by oxidation of a sulfur trioxide-pyridine complex salt

To a solution of 80 mg (0.32 mmol) of Compound No. III-1 in 4 mℓ of dimethylsulfoxide dehydrated by molecular sieves, a solution of 304 mg (1.91 mmol) of a sulfur trioxide-pyridine complex salt and 196 mg (1.94 mmol) of triethylamine in 4 mℓ of dimethylsulfoxide dehydrated by molecular sieves, was dropwise added, and the mixture was stirred at room temperature for 4 hours. Ice water was added thereto, and the mixture was extracted with ethyl acetate. Then, the organic layer was dried over anhydrous sodium sulfate, and the drying agent was filtered off. Then, the solvent was distilled off under reduced pressure. The residue thereby obtained was subjected to thin layer chromatography (developer:

ethyl acetate/hexane = 1/1) to obtain 39 mg (48.9%) of the desired substance (Compound No. II-1) as colorless oil and 3 mg (4.0%) of Compound No. II-7 as colorless needles.

Step 4

5-((5-(2-Hydroxy-2-phenylethoxy)-1-methyl-3-pyrazolyl)methylidene)thiazolidin-2,4-dione (Compound No. I-1a-1)



(I-1a-1)

1.53 g (6.21 mmol) of Compound No. II-1 and 974 mg of thiazolidinedione were suspended in 60 mℓ of toluene. To this solution, 108 μℓ of glacial acetic acid and then 122 μℓ of piperidine were added, and the mixture was stirred at 130°C for 140 minutes. After confirming disappearance of the starting material by thin layer chromatography, the solvent was distilled off under reduced pressure. The residue thereby obtained was dissolved in tetrahydrofuran/chloroform. This solution was washed with a saturated sodium chloride aqueous solution and then dried over anhydrous magnesium sulfate. The drying agent was filtered off. Then, the solvent was distilled off under reduced pressure. The residue thereby obtained was subjected to silica gel column chromatography (eluent: tetrahydrofuran/hexane = 1/2) and then to thin

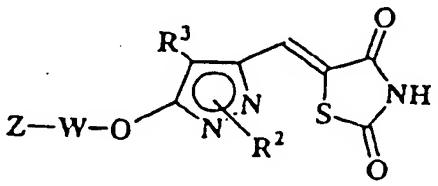
layer chromatography (developer: tetrahydrofuran/hexane = 1/2) to obtain 2.11 g (98.3%) of the desired substance (Compound No. I-1a-1) as colorless powder.

mp 172.8-174.3°C

MS(EI) m/e: 345$(M)^+$

500 MHz ^{1}H-NMR(d^6-acetone)δ: 3.70(3H, s), 4.21(1H, dd, $^2J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 7.6 Hz), 4.27(1H, dd, $^2J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 3.9 Hz), 4.94(1H, d, $^3J_{HH}$ = 4 Hz), 5.15(1H, ddd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 3.9 Hz, $^3J_{HH}$ = 4 Hz), 5.77(1H, s), 7.30(1H, t, $^3J_{HH}$ = 7.3 Hz), 7.38(2H, dd, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 7.6 Hz), 7.51(1H, s), 7.52(2H, d, $^3J_{HH}$ = 7.6 Hz), 12.3(1H, s)

In the same manner, Compounds Nos. I-1a-2 to I-1a-14 were prepared by using Compounds Nos. II-2 to II-14 as starting materials. (R^2, R^3, W and Z in the Table correspond to the substituents of Compound No. 1-1a.)



(I-1a)
R^1=O-W-Z
R^6=H

Starting material	Compound No.	R^2	R^3	Z-W
II-2	I-1a-2	1-Me	H	$PhCH_2CH_2$
II-3	I-1a-3	1-t-Bu	H	$PhCH(OH)CH_2$
II-4	I-1a-4	1-t-Bu	H	$PhCOCH_2$

II-5	I-1a-5	1-Ph	H	$PhCH(OH)CH_2$
II-6	I-1a-6	1-Me	H	5-Me-2-Ph-4-oxazolyl-$CH(OH)CH_2$
II-7	I-1a-7	1-Me	H	$PhCOCH_2$
II-8	I-1a-8	1-Me	H	5-Me-2-Ph-4-oxazolyl-$COCH_2$
II-9	I-1a-9	1-t-Bu	H	5-Me-2-Ph-4-oxazolyl-$COCH_2$
II-10	I-1a-10	1-Ph	H	5-Me-2-Ph-4-oxazolyl-$COCH_2$
II-11	I-1a-11	1-Me	H	3-Me-2-benzo[b]thiophenyl-$COCH_2$
II-12	I-1a-12	1-Me	H	2-benzo[b]furanyl-$COCH_2$
II-13	I-1a-13	1-Me	H	5-Me-1-Ph-4-pyrazolyl-$COCH_2$
II-14	I-1a-14	1-Me	H	3-Br-1-Me-2-indolyl-$COCH_2$

Compound No.	Properties	mp (°C)	MS (m/e)
I-1a-2	Pale yellow powder	158-161	329(M)$^+$EI
I-1a-3	Colorless crystals	108.4-110.6	387(M)$^+$EI
I-1a-4	Pale brown crystals	216.8-218.7	385(M)$^+$EI
I-1a-5	Pale brown crystals	192.4-194.5	407(M)$^+$EI
I-1a-6	Colorless crystals	185-187	426(M)$^+$EI

I-1a-7	Colorless powder	214-216	344(M+H)$^+$FAB
I-1a-8	Pale brown crystals	208-211	424(M)$^+$EI
I-1a-9	Brown crystals	213-216	466(M)$^+$EI
I-1a-10	Yellowish brown powder	275-280 (decomp.)	486(M)$^+$EI
I-1a-11	Pale brown powder	258-260	413(M)$^+$EI
I-1a-12	Pale brown powder	250-260 (decomp.)	383(M)$^+$EI
I-1a-13	Pale brown powder	236-240	424(M+H)$^+$FAB
I-1a-14	Brown powder	243-246	475(M+H)$^+$FAB

Compound No. (I-1a-2)

500 MHz ^{1}H-NMR(d^6-DMSO)δ: 3.06(2H, t, $^3J_{HH}$ = 6.7 Hz), 3.59(3H, s), 4.31(2H, t, $^3J_{HH}$ = 6.7 Hz), 6.12(1H, s), 7.24-7.48(5H, m), 7.48(1H, s),12.3(1H, br s)

Compound No. (I-1a-3)

500 MHz ^{1}H-NMR($CDCl_3$)δ: 1.58(9H, s), 2.35(1H, d, $^3J_{HH}$ = 3.2 Hz), 4.18(2H, m), 5.15(1H, m), 5.77(1H, s), 7.36-7.45(5H, m), 7.56(1H, s), 8.20(1H, s)

Compound No. (I-1a-4)

500 MHz ^{1}H-NMR(d^6-DMSO)δ: 1.63(9H, s), 5.70(2H, s), 6.15(1H, s), 7.44(1H, s), 7.58(2H, dd, $^3J_{HH}$ = 7.4, 7.8 Hz), 7.71(1H, t, $^3J_{HH}$ = 7.4 Hz), 8.00(2H, d, $^3J_{HH}$ = 7.8 Hz), 12.26(1H, s)

Compound No. (I-1a-5)

500 MHz ^{1}H-NMR($CDCl_3$)δ: 2.40(1H, d), 4.29(2H, d), 5.17(1H, m), 5.91(1H, s), 7.23-7.46(8H, m), 7.62(1H, s), 7.75(2H, d, $^3J_{HH}$ = 7.6 Hz), 8.12(1H, br s)

Compound No. (I-1a-6)

500 MHz ^{1}H-NMR(d^6-DMSO)δ: 2.50(3H, s), 3.65(3H, s), 4.31(2H, d, $^3J_{HH}$ = 5.4 Hz), 4.97(1H, dt, $^3J_{HH}$ = 4.9 Hz, $^3J_{HH}$ = 5.4 Hz), 5.75(1H, d, $^3J_{HH}$ = 4.9 Hz), 6.12(1H, s), 7.47(1H, s), 7.50(3H, m), 7.92(2H, d, $^3J_{HH}$ = 8.1 Hz), 12.3(1H, s)

Compound No. (I-1a-7)

500 MHz ^{1}H-NMR(d^6-DMSO)δ: 3.76(3H, s), 5.74(2H, s), 6.11(1H, s), 7.44(1H, s), 7.58(2H, t, $^3J_{HH}$ = 7.3, 7.7 Hz), 7.71(1H, t, $^3J_{HH}$ = 7.7 Hz), 7.88(2H, d, $^3J_{HH}$ = 7.3 Hz), 12.4(1H, br s)

Compound No. (I-1a-8)

500 MHz ^{1}H-NMR($CDCl_3$)δ: 2.74(3H, s), 3.87(3H, s), 5.41(2H, s), 5.76(1H, s), 7.49-7.52(3H, m), 7.56(1H, s), 8.03-8.05(2H, m), 8.14(1H, br s)

Compound No. (I-1a-9)

500 MHz ^{1}H-NMR($CDCl_3$)δ: 1.71(9H, s), 2.75(3H, s), 5.39(2H, s), 5.81(1H, s), 7.50-7.51(3H, m), 7.56(1H, s), 8.04-8.06(2H, m), 8.08(1H, br s)

Compound No. (I-1a-10)

500 MHz ^{1}H-NMR($CDCl_3$)δ: 2.71(3H, s), 5.68(2H, s), 6.38(1H, s), 7.41(1H, t, $^3J_{HH}$ = 7.3 Hz), 7.52(1H, s), 7.56-7.60(5H, m), 7.91-7.93(2H, m), 8.02-8.04(2H, m), 12.4(1H, br s)

Compound No. (I-1a-11)

500 MHz ^{1}H-NMR(d^6-DMSO)δ: 2.77(3H, s), 3.77(3H, s), 5.62(2H, s), 6.16(1H, s), 7.44(1H, s), 7.53(1H, dd, $^3J_{HH}$

= 7.2, 8.3 Hz), 7.60(1H, dd, $^3J_{HH}$ = 7.2, 8.3 Hz), 8.07(1H, d, $^3J_{HH}$ = 8.3 Hz), 8.09(1H, d, $^3J_{HH}$ = 8.3 Hz), 12.4(1H, br s)

Compound No. (I-1a-12)

500 MHz ^{1}H-NMR(d^6-DMSO)δ: 3.77(3H, s), 5.64(2H, s), 6.16(1H, s), 7.41(1H, dd, $^3J_{HH}$ = 7.1, 7.9 Hz), 7.45(1H, s), 7.60(1H, dd, $^3J_{HH}$ = 7.1, 8.3 Hz), 7.77(1H, d, $^3J_{HH}$ = 8.3 Hz), 7.90(1H, d, $^3J_{HH}$ = 7.9 Hz), 8.06(1H, s), 12.4(1H, br s)

Compound No. (I-1a-13)

500 MHz ^{1}H-NMR(d^6-DMSO)δ: 2.52(3H, s), 3.76(3H, s), 5.47(2H, s), 6.10(1H, s), 7.46(1H, s), 7.52-7.60(5H, m), 8.37(1H, s), 12.4(1H, br s)

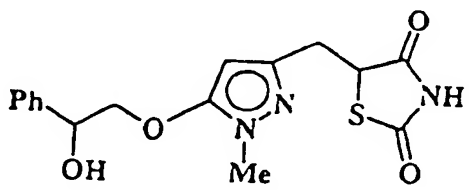
Compound No. (I-1a-14)

500 MHz ^{1}H-NMR(d^6-DMSO)δ: 3.76(3H, s), 3.96(3H, s), 5.69(2H, s), 6.16(1H, s), 7.30(1H, dd, $^3J_{HH}$ = 7.3, 7.9 Hz), 7.46(1H, s), 7.50(1H, dd, $^3J_{HH}$ = 7.3, 8.5 Hz), 7.64(1H, d, $^3J_{HH}$ = 7.9 Hz), 7.70(1H, d, $^3J_{HH}$ = 8.5 Hz), 12.3(1H, br s)

EXAMPLE 2

Step 5

Preparation of 5-((5-(2-hydroxy-2-phenylethoxy)-1-methyl-3-pyrazolyl)methyl)thiazolidin-2,4-dione (Compound No. I-2a-1)



(I-2a-1)

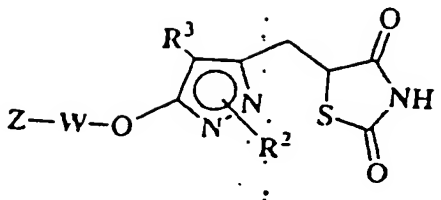
348 mg (1.01 mmol) of 5-((5-(2-hydroxy-2-phenylethoxy)-1-methyl-3-pyrazolyl)methylidene)thiazolidin-2,4-dione (Compound No. I-1a-1) was dissolved in 15 mℓ of tetrahydrofuran dehydrated by molecular sieves. To this solution, 271 mg of 10% palladium carbon was added, followed by catalytic reduction at room temperature under hydrogen pressure of 5 atm for 48.5 hours. The catalyst was filtered off. Then, the solvent was distilled off under reduced pressure. The residue thereby obtained was subjected to silica gel column chromatography (eluent: 6% methanol/chloroform) to obtain 363 mg (quantitative) of the desired substance (Compound No. I-2a-1) as colorless powder.

mp 68-71°C

MS(EI) m/e: 347$(M)^+$

60 MHz ^{1}H-NMR($CDCl_3$)δ: 3.23(2H, m), 3.54(3H, s), 4.10(2H, d), 4.56(1H, dd), 5.08(1H, t), 5.37(1H, s), 7.36(5H, s)

In the same manner, Compounds Nos. I-2a-2 to I-2a-8 were prepared by using Compounds Nos. I-1a-2 to I-1a-6, I-1a-11 and I-1a-12 as starting materials. (R^2, R^3, W and Z in the Table correspond to the substituents of Compound No. I-2a.)



(I-2a)
R^1=O-W-Z
R^6=H

Starting material	Compound No.	R^2	R^3	Z-W
I-1a-2	I-2a-2	1-Me	H	$PhCH_2CH_2$
I-1a-3	I-2a-3	1-t-Bu	H	$PhCH(OH)CH_2$
I-1a-4	I-2a-4	1-t-Bu	H	$PhCOCH_2$
I-1a-5	I-2a-5	1-Ph	H	$PhCH(OH)CH_2$
I-1a-6	I-2a-6	1-Me	H	5-Me-2-Ph-4-oxazolyl-$CH(OH)CH_2$
I-1a-11	I-2a-7	1-Me	H	3-Me-2-benzo[b]-thiophenyl-$COCH_2$
I-1a-12	I-2a-8	1-Me	H	5-Me-1-Ph-4-pyrazolyl-$COCH_2$

Compound No.	Properties	mp (°C)	MS (m/e)
I-2a-2	Pale yellow powder	103-105	331$(M)^+$EI
I-2a-3	Pale yellow oil		389$(M)^+$EI
I-2a-4	Brown solid		387$(M)^+$EI
I-2a-5	Pale yellow amorphous		409$(M)^+$EI
I-2a-6	Colorless solid	95-97	428$(M)^+$EI
I-2a-7	Colorless solid	211-212	414$(M)^+$EI
I-2a-8	Colorless solid	140-142	425$(M)^+$EI

Compound No. (I-2a-2)

500 MHz ^{1}H-NMR($CDCl_3$)δ:2.95(2H, t), 3.0-3.5(2H, m), 3.43(3H, s), 4.08(2H, t), 4.5(1H, m), 5.27(1H, s), 7.14(5H, s), 7.60(1H, br s)

Compound No. (I-2a-3)

500 MHz ^{1}H-NMR($CDCl_3$)δ: 1.50(9H, s), 3.06(1H, m), 3.44(1H, m), 4.11(2H, m), 4.66(1H, m), 5.11(1H, m), 5.40(1H, s), 7.3-7.5(5H, m), 8.89(1H, s), 9.08(1H, br s)

Compound No. (I-2a-4)

500 MHz ^{1}H-NMR($CDCl_3$)δ: 1.4(9H, s), 3.00-3.07(1H, m), 3.40-3.46(1H, m), 4.65-4.70(1H, m), 5.25(2H, s), 5.38(1H, s), 7.50-7.55(2H, m), 7.63-7.65(1H, m), 7.95-7.98(2H, m), 8.45(1H, s)

Compound No. (I-2a-5)

500 MHz ^{1}H-NMR($CDCl_3$)δ: 2.45(1H, br s), 3.16(1H, m), 3.56(1H, m), 4.20-4.21(2H, m), 4.75(1H, m), 5.13(1H, m), 5.56(1H, s), 7.25-7.42(8H, m), 7.61(1H, m), 8.10(1H, s)

Compound No. (I-2a-6)

500 MHz ^{1}H-NMR($CDCl_3$)δ: 2.42(3H, s), 3.11(1H, dd), 3.41(1H, dd), 3.58(3H, s), 4.22(1H, dd), 4.35(1H, dd), 4.61(1H, dd), 5.04(1H, dd), 5.44(1H, s), 7.43(3H, m), 7.97(2H, m), 9.0(1H, s)

Compound No. (I-2a-7)

500 MHz ^{1}H-NMR(d^6-DMSO)δ: 2.75(3H, s), 2.95(1H, dd, $^2J_{HH}$ = 15.5 Hz, $^3J_{HH}$ = 10.6 Hz), 3.24(1H, dd, $^2J_{HH}$ = 15.5 Hz, $^3J_{HH}$ = 3.6 Hz), 3.59(3H, s), 4.77(1H, dd, $^3J_{HH}$ = 3.6, 10.6 Hz), 5.49(2H, s), 5.62(1H, s), 7.52(1H, dd, $^3J_{HH}$ =

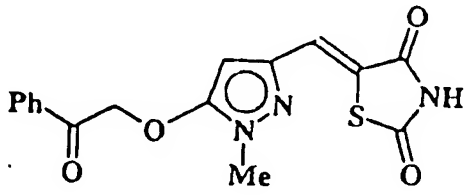
7.1, 8.1 Hz), 7.59(1H, dd, $^3J_{HH}$ = 7.1, 8.2 Hz), 8.06(1H, d, $^3J_{HH}$ = 8.2 Hz), 8.08(1H, d, $^3J_{HH}$ = 8.1 Hz), 12.0(1H, br s)

Compound No. (I-2a-8)

500 MHz ^{1}H-NMR(d^6-DMSO)δ: 2.52(3H, s), 2.97(1H, m), 3.26(1H, m), 3.58(3H, s), 4.78(1H, m), 5.34(2H, s), 5.56(1H, s), 7.54-7.59(5H, m), 8.35(1H, s), 12.0(1H, br s)

EXAMPLE 3

Preparation of 5-((1-methyl-5-phenacyloxy-3-pyrazolyl)methylidene)thiazolidin-2,4-dione (Compound No. I-1a-7)



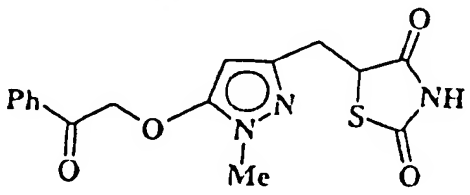
(I-1a-7)

127 mg (0.367 mmol) of 5-((5-(2-hydroxy-2-phenylethoxy)-1-methyl-3-pyrazolyl)methylidene)thiazolidin-2,4-dione (Compound No. I-1a-1) was dissolved in 6 mℓ of dichloromethane dehydrated by molecular sieves, together with 114 mg (0.527 mmol) of pyridinium chlorochromate and 549 mg of celite, and the mixture was stirred at 0°C for 40 minutes and then at room temperature for 3.75 hours under a nitrogen atmosphere. Further, 90 mg (0.42 mmol) of pyridinium chlorochromate was added thereto, and the

mixture was stirred at room temperature overnight. The inorganic salt was filtered off. Then, the solvent was distilled off. The residue thereby obtained was subjected to silica gel column chromatography (eluent: ethyl acetate/benzene = 1/2) to obtain 120 mg (95.5%) of the desired substance (Compound No. I-1a-7) as colorless powder.

EXAMPLE 4

Preparation of 5-((1-methyl-5-phenacyloxy-3-pyrazolyl)methyl)thiazolidin-2,4-dione (Compound No. I-2a-9)



(I-2a-9)

204 mg (0.946 mmol) of pyridinium chlorochromate, 96 mg of anhydrous sodium acetate and 503 mg of celite were suspended in 10 mℓ of dichloromethane dehydrated by molecular sieves. To this suspension, a solution of 135 mg (0.390 mmol) of 5-((5-(2-hydroxy-2-phenylethoxy)-1-methyl-3-pyrazolyl)methyl)thiazolidin-2,4-dione (Compound No. I-2a-1) in 5 mℓ of dichloromethane dehydrated by molecular sieves, was dropwise added. The mixture was stirred at 0°C for 1.5 hours and then at room temperature for 1.75 hours. Then, the inorganic salt was filtered off, and the solvent was distilled off under reduced

pressure. The residue thereby obtained was subjected to silica gel column chromatography (eluent: 4% methanol/chloroform), followed by recrystallization from ethyl acetate/hexane to obtain 69 mg (51.2%) of the desired substance (Compound No. I-2a-9) as colorless crystals.

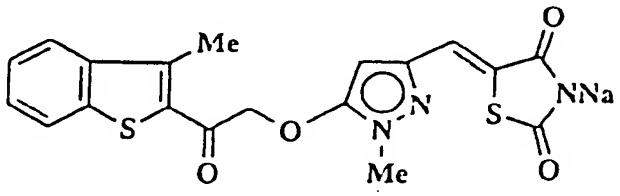
mp 141-143°C

MS(EI) m/e: 345$(M)^+$

500 MHz ^{1}H-NMR($CDCl_3$)δ: 3.06(1H, dd, $^2J_{HH}$ = 15.4 Hz, $^3J_{HH}$ = 10.0 Hz), 3.44(1H, dd, $^2J_{HH}$ = 15.4 Hz, $^3J_{HH}$ = 3.8 Hz), 3.68(3H, s), 4.63(1H, dd, $^3J_{HH}$ = 3.8 Hz, $^3J_{HH}$ = 10.0 Hz), 5.27(2H, s), 5.35(1H, s), 7.52(1H, dd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 7.9 Hz), 7.64(1H, t, $^3J_{HH}$ = 7.6 Hz), 7.94(2H, d, $^3J_{HH}$ = 7.9 Hz), 8.33(1H, br s)

EXAMPLE 5

Preparation of sodium salt of 5-((1-methyl-5-(2-(3-methylbenzo[b]thiophen-2-yl)-2-oxoethoxy)-3-pyrazolyl)methylidene)thiazolidin-2,4-dione (Compound No. I-1a-11-Na)



(I-1a-11-Na)

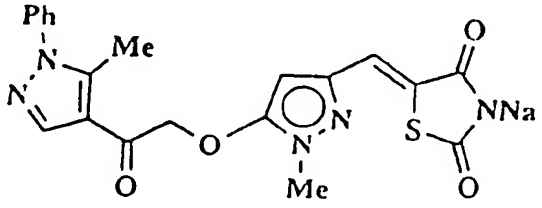
69 mg (0.17 mmol) of 5-((1-methyl-5-(2-(3-methylbenzo[b]thiophen-2-yl)-2-oxoethoxy-3-pyrazolyl)methylidene)thiazolidin-2,4-dione (Compound No.

I-1a-11) was dissolved in 5 mℓ of tetrahydrofuran and 3 mℓ of chloroform. To this solution, 0.32 mℓ (0.17 mmol) of an aqueous solution of 0.5 mol/ℓ of sodium hydroxide was dropwise added at room temperature. The solvent was distilled off under reduced pressure. Then, 5 mℓ of deionized water was added, and the solution thereby obtained was freeze-dried to obtain 69 mg (94.9%) of the desired substance (Compound No. I-1a-11-Na) as pale brown powder.

mp 180-240°C (decomp.)

MS(FAB) m/e: 436$(M+H)^+$

In the same manner, Compounds Nos. I-1a-13-Na, I-2a-7-Na and I-2a-8-Na were prepared by using Compounds Nos. I-1a-13, I-2a-7 and I-2a-8, respectively, as starting materials.



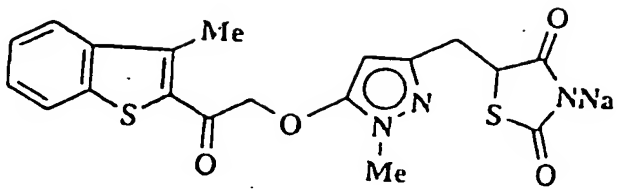
(I-1a-13-Na)

Compound No. I-1a-13-Na

Colorless powder

mp 200-220°C (decomp.)

MS(FAB) m/e: 446$(M+H)^+$



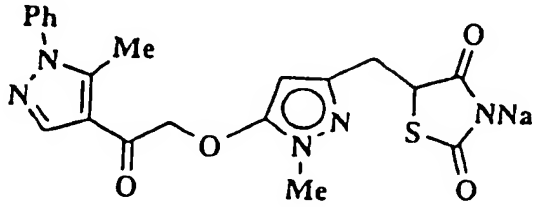
(I-2a-7-Na)

Compound No. I-2a-7-Na

Pale pink powder

mp 90-110°C (decomp.)

MS(FAB) m/e: 438(M+H)$^+$



(I-2a-8-Na)

Compound No. I-2a-8-Na

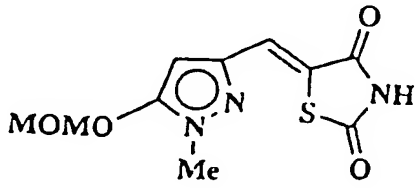
Colorless powder

mp 185-220°C (decomp.)

MS(FAB) m/e: 448(M+H)$^+$

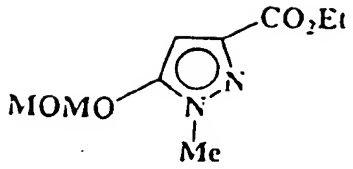
EXAMPLE 6

Preparation of 5-((5-methoxymethoxy-1-methyl-3-pyrazolyl)methylidene)thiazolidin-2,4-dione (Compound No. XII-1-1)



(XII-1-1)

Ethyl 5-methoxymethoxy-1-methyl-3-pyrazolecarboxylate (Compound No. XV-1)



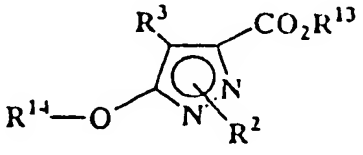
(XV-1)

In the same manner as in Step 1 in Example 1, 3.09 g (81.8%) of the desired substance (Compound No. XV-1) was obtained as pale yellow oil by using 3.00 g (17.6 mmol) of ethyl 5-hydroxy-1-methyl-3-pyrazolecarboxylate (Compound No. V-1), 2.0 mℓ (26 mmol) of chloromethyl methyl ether and 4.0 mℓ (23 mℓ) of diisopropylethylamine.

MS(EI) m/e: 214$(M)^+$

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.38(3H, t), 3.49(3H, s), 3.74(3H, s), 4.35(2H, q), 5.13(2H, s), 6.17(1H, s)

In the same manner, Compounds Nos. XV-2 and XV-3 were prepared using Compound No. V-1 as starting material. (R^2, R^3, R^{13} and R^{14} in the Table correspond to the substituents of Compound No. XV.)



(XV)
R^1=O-R^{14}

Compound No.	R^2	R^3	R^{13}	R^{14}
XV-2	1-Me	H	Et	$MeOCH_2CH_2OCH_2$
XV-3	1-Me	H	Et	t-Bu$(Me)_2$Si

Compound No.	Properties	mp (°C)	MS (m/e)
XV-2	Pale yellow oil		258(M)$^+$EI
XV-3	Pale yellow oil		284(M)$^+$EI

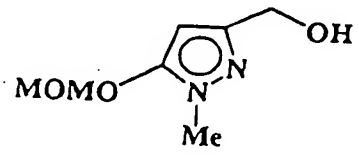
XV-2

60 MHz ^{1}H-NMR($CDCl_3$)δ: 1.39(3H, t), 3.42(3H, s), 3.75(3H, s), 3.4-3.9(4H, m), 4.39(2H, q), 5.25(2H, s), 6.22(1H, s)

XV-3

60 MHz ^{1}H-NMR($CDCl_3$)δ: 0.28(6H, s), 1.00(9H, s), 1.37(3H, t), 3.70(3H, s), 4.28(2H, q), 5.89(1H, s)

3-Hydroxymethyl-5-methoxymethoxy-1-methylpyrazole (Compound No. XIV-1)



(XIV-1)

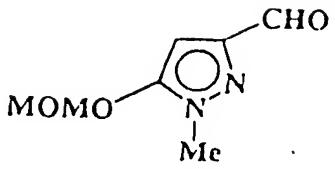
In the same manner as in Step 2 in Example 1, 54 mg (64%) of the desired substance (Compound No. XIV-1) was obtained as pale yellow oil by using 105 mg (0.488 mmol) of Compound No. XV-1 and 108 mg (2.83 mmol) of lithium aluminum hydride.

MS(FAB) m/e: 173$(M+H)^+$

60 MHz ^{1}H-NMR($CDCl_3$)δ: 2.6(1H, br), 3.47(3H, s), 3.62(3H, s), 4.53(2H, s), 5.10(2H, s), 5.65(1H, s)

5-Methoxymethoxy-1-methylpyrazole-3-carbaldehyde

(Compound No. XIII-1)



(XIII-1)

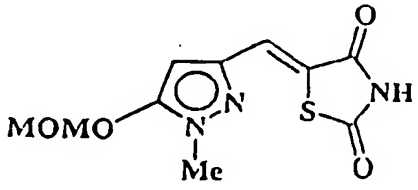
In the same manner as the Swern oxidation shown in Step 3 in Example 1, 132 mg (95.2%) of the desired substance (Compound No. XIII-1) was obtained as pale brown oil by using 141 mg (0.817 mmol) of Compound No. XIV-1, 277 μℓ (3.18 mmol) of oxalyl chloride, 622 mg (7.96 mmol) of dimethylsulfoxide dehydrated by molecular sieves and 2.2 mℓ (16 mmol) of triethylamine dehydrated by molecular sieves.

This compound was obtained also by the manganese dioxide oxidation method and the PCC oxidation method shown in Step 3 in Example 1.

MS(FAB) m/e: 171$(M+H)^+$

60 MHz ^{1}H-NMR($CDCl_3$)δ: 3.50(3H, s), 3.77(3H, s), 5.12(2H, s), 6.16(1H, s), 9.74(1H, s)

5-((5-Methoxymethoxy-1-methyl-3-pyrazolyl)methylidene)-thiazolidin-2,4-dione (Compound No. XII-1-1)



(XII-1-1)

In the same manner as in Step 4 in Example 1, 337 mg (99.9%) of the desired substance (Compound No. XII-1-1)

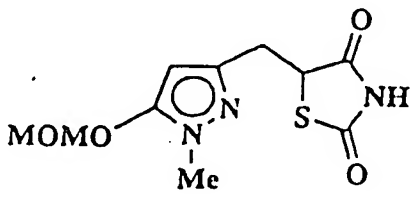
was obtained as pale brown needles by using 213 mg (1.25 mmol) of Compound No. XIII-1, 164 mg (1.26 mmol) of thiazolidinedione (Compound No. VI-1) , 25 $\mu\ell$ of piperidine and 22 $\mu\ell$ of acetic acid.

mp 161-164°C

MS(EI) m/e: 269$(M)^+$

60 MHz ^{1}H-NMR($CDCl_3$)δ: 3.52(3H, s), 3.76(3H, s), 5.16(2H, s), 5.92(1H, s), 7.30(1H, t, $^3J_{HH}$ = 7.3 Hz), 7.38(2H, dd, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 7.6 Hz), 7.59(1H, s), 8.17(1H, br s)

Preparation of 5-((5-methoxymethoxy-1-methyl-3-pyrazolyl)methyl)thiazolidin-2,4-dione (Compound No. XII-2-1)



(XII-2-1)

In the same manner as in Example 2, 167 mg (quantitative) of the desired substance (Compound No. XII-2-1) was obtained as pale yellow powder by using 144 mg (0.533 mmol) of 5-((5-methoxmethoxy-1-methyl-3-pyrazolyl)methylidene)thiazolidin-2,4-dione (Compound No. XII-1-1) and 129 mg of 10% palladium carbon.

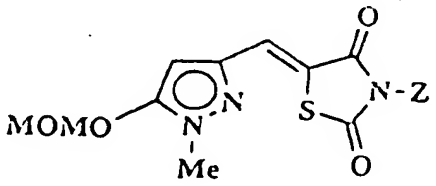
mp 114-117°C

MS(EI) m/e: 271$(M)^+$

60 MHz ^{1}H-NMR($CDCl_3$)δ: 3.09-3.5(2H, m), 3.46(3H, s), 3.61(3H, s), 4.48-4.72(1H, m), 5.05(2H, s), 5.51(1H, s),

10.13(1H, br s)

Protection by Z group (benzyloxycarbonyl) of 5-((5-methoxymethoxy-1-methyl-3-pyrazolyl)methylidene)-thiazolidin-2,4-dione (Compound No. XII-1-1)



(XII-1-2)

To a solution of 81 mg (0.30 mmol) of 5-((5-methoxymethoxy-1-methyl-3-pyrazolyl)methylidene)thiazolidin-2,4-dione (Compound No. XII-1-1) in 10 mℓ of tetrahydrofuran dehydrated by molecular sieves, 49 mg (0.46 mmol) of anhydrous sodium carbonate and then 64 μℓ (0.45 mmol) of benzyl chloroformate were added at room temperature, and the reaction solution was stirred overnight. To this solution, 5 mℓ of a saturated sodium chloride aqueous solution was added, and the mixture was extracted with 45 mℓ of ethyl acetate. Then, the organic layer was dried over anhydrous sodium sulfate. The drying agent was filtered off. Then, the solvent was distilled off under reduced pressure. The residue thereby obtained was recrystallized from ethyl acetate and hexane to obtain 71 mg (59%) of the desired substance (Compound No. XII-1-2) as colorless crystals.

MS(EI) m/e: 403$(M)^+$

500 MHz ^{1}H-NMR($CDCl_3$)δ: 3.53(3H, s), 3.77(3H, s),

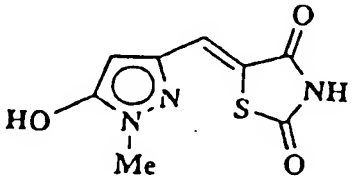
5.14(2H, s), 5.46(2H, s), 5.92(1H, s), 7.42(5H, s), 7.66(1H, s)

REFERENCE EXAMPLE 1

Removal of protective Z group of Compound No. XII-1-2

19 mg (0.047 mmol) of Compound No. XII-1-2 was dissolved in 10 mℓ of tetrahydrofuran dehydrated by molecular sieves. To this solution, 6 mg of 10% palladium carbon was added, followed by catalytic reduction at room temperature under a hydrogen pressure of 1 atm overnight and then for 3 days by an addition of 6 mg of the catalyst. The catalyst was filtered off, and then the solvent was distilled off under educed pressure. The residue thereby obtained was subjected to thin layer chromatography (developer: 5% methanol/chloroform) to obtain 16 mg (quantitative) of the desired substance (Compound No. XII-1-1) as pale brown powder.

Preparation of 5-((5-hydroxy-1-methyl-3-pyrazolyl)methylidene)thiazolidin-2,4-dione (Compound No. X-1-1) (Removal of protective MOM group)



(X-1-1)

To a solution of 54 mg (0.20 mmol) of 5-((5-methoxymethoxy-1-methyl-3-pyrazolyl)methylidene)thiazolidin-2,4-dione (Compound No.

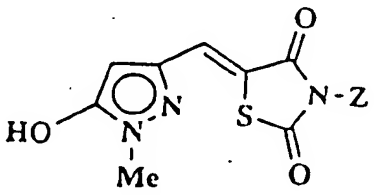
XII-1-1) in 5 mℓ of tetrahydrofuran and 1 mℓ of methanol, one drop of concentrated hydrochloric acid was added at room temperature, and the reaction solution was stirred at 56°C for 5 hours. To the reaction solution, toluene was added, and the solvent was distilled off under reduced pressure. The residue thereby obtained was recrystallized from methanol to obtain 31 mg (69%) of the desired substance (Compound No. X-1-1) as yellow crystals.

mp 248-250°C (decomp.)

MS(EI) m/e: $225(M)^+$

500 MHz ^{1}H-NMR($CDCl_3$)δ: 3.61(3H, s), 5.76(1H, s), 7.46(1H, s), 11.5(1H, br), 12.3(1H, br)

In the same manner, Compound No. X-1-2 was prepared by using Compound (XII-1-2) as starting material.



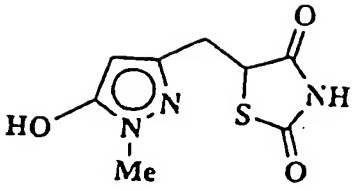
(X-1-2)

Pale yellow powder

mp 153-158°C (decomp.)

MS(FAB) m/e: $360(M+H)^+$

In the same manner, Compound No. X-2-1 was prepared by using Compound No. XII-2-1 as starting material.



(X-2-1)

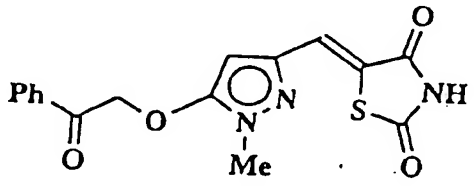
Pale yellow crystals

mp 150-154°C

MS(FAB) m/e: 228$(M+H)^+$

EXAMPLE 7

Preparation of 5-((1-methyl-5-phenacyloxy-3-pyrazolyl)methylidene)thiazolidin-2,4-dione (Compound No. 1-1a-7)



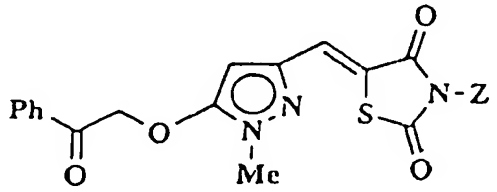
(I-1a-7)

69 mg (0.31 mmol) of 5-((5-hydroxy-1-methyl-3-pyrazolyl)methylidene)thiazolidin-2,4-dione (Compound No. X-1-1) and 57 mg (0.37 mmol) of phenacyl chloride were dissolved in 2 mℓ of dimethylformamide dehydrated by molecular sieves. To this solution, 65 μℓ of triethylamine was added, and the mixture was stirred at room temperature overnight. To this reaction solution, 1 mℓ of a saturated sodium chloride aqueous solution was added, and the mixture was extracted with 120 mℓ of ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then the solvent was distilled off under reduced

pressure. The residue thereby obtained was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 5/6) to obtain 17 mg (16%) of the desired substance (Compound No. 1-1a-7) as pale yellow powder.

In the same manner, Compound No. I-2a-9 was prepared by using Compound No. X-2-1 by the reaction with phenacyl chloride.

Further, using Compound No. X-1-2 (Z group protected product of Compound No. X-1-1) as starting material, R^1 substituent was introduced in the same manner to obtain Compound No. XVIII-1, followed by removal of the protective group in the same manner as in Example 6 to obtain the desired Compound No. I-1a-7.



(XVIII-1)

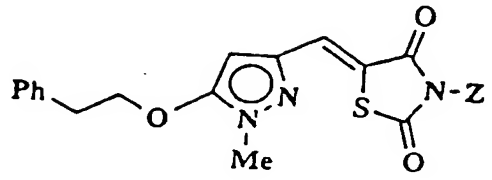
Pale yellow powder (yield: 16.6%)

MS(EI) m/e: 477$(M)^+$

500 MHz ^{1}H-NMR($CDCl_3$)δ: 3.80(3H, s), 5.15(2H, s), 5.33(2H, s), 6.42(1H, s), 7.36-7.63(8H, m), 7.70(1H, s), 7.99(2H, m)

In the same manner, using Compound No. X-1-2 and phenetyl bromide as starting materials, Z group protected product of Compound I-1a-2 (Compound No. XVIII-2) was prepared, followed by removal of the protective group in

the same manner as in Example 6 to obtain the desired Compound I-1a-2.



(XVIII-2)

Pale brown powder (yield: 35.1%)

MS(EI) m/e: 463$(M)^+$

500 MHz ^{1}H-NMR($CDCl_3$)δ: 2.96(2H, t, $^3J_{HH}$ = 7.8 Hz), 3.78(3H, s), 3.95(2H, t, $^3J_{HH}$ = 7.8 Hz), 5.32(2H, s), 6.39(1H, s), 7.21-7.45(10H, m), 7.62(1H, s)

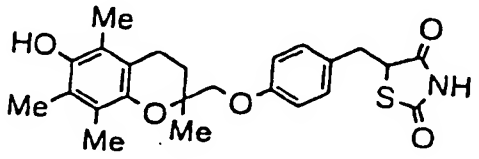
TEST EXAMPLE 1: Measurement of hypoglycemic effect

KK mouse and KKA^{y} mouse, NIDDM models (male, 6-7 weeks old) (Nakamura, Proc. Jpn. Acad. 38, 348-352, 1962; Iwatsuka et al. Endocrinol. Jpn., 17, 23-35, 1970) were purchased from Nihon Clea. They were allowed free access to high-calories' chow (CMF, Oriental Yeast) and water. Around 40 g-weighted mice were examined.

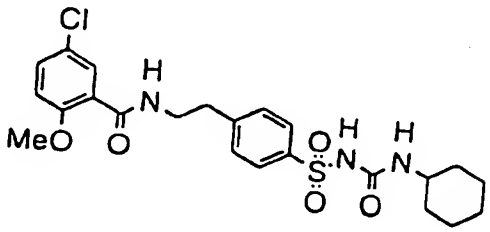
Blood (20 $\mu\ell$) collected from the retro-orbital sinus was diluted in 60 units heparin sodium-solution and was centrifuged in a microfuge. The supernatant was assayed. The glucose concentration was determined by glucose oxidase method (Glucose Analyzer II, Beckman). A group of 3 to 4 mice having a blood glucose value of higher than 200 mg/dℓ, the blood glucose value of which did not reduce by more than 10% for 24 hours after once oral administration of 0.5% carboxymethyl cellulose (CMC)-saline, were tested.

All test-compounds suspended in 0.5% carboxy-methyl cellulose (CMC)-saline were orally administered in mice. Before and 24 hours after the administration, blood was collected from the retro-orbital sinus, and a blood glucose value was measured in the above-mentioned manner. The hypoglycemic activity was expressed by the percentage of reducing blood glucose calculated before and 24 hours after the administration.

Compound No.	Dose (mg/kg)	% decrease
I-1a-2	30	15.1
I-1a-5	30	3.8
I-1a-6	30	22.1
I-1a-9	30	35.9
I-1a-11-Na	30	11.1
I-1a-12	30	6.4
I-2a-1	30	3.2
I-2a-3	30	24.1
I-2a-4	30	10.8
I-2a-5	30	10.5
I-2a-6	30	12.9
CS-045	30	-3.0
Glibenclamide	30	-2.5



CS-045



Glibenclamide

The compounds of the present invention exhibited hypoglycemic activities at substantially the same or higher degree as compared with CS-045 and CP-86325 used as controls. Glibenclamide (insulin-releasing agent) did

not exhibit hypoglycemic activity in this test.

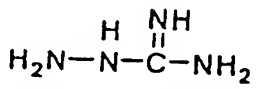
TEST EXAMPLE 2: Measurement of anti-glycation effect

When high-glucose concentrations in diabetic patients sustain for a long time, some kinds of proteins are glycated non-enzymatically. It is considered that the glycated proteins induce diabetic complications (Brownlee, Diabetes, 41 suppl 2, 57-60, 1992).

Because glycated protein is fluorescent, the amount of glycated protein can be determined using fluorescence, according to the previous reports (Doi et al., Proc. Natl. Acad. Sci. U.S.A., 89, 2873-2877, 1992: Mitsuhashi et al., Diabetes, vol. 42, 826-832, 1993). The experimental procedure was modified as follows. Five percent of bovine serum albumin (BSA) containing 0.5M glucose-6-phosphate-2Na (5% BSA-0.5M G6P) was filtration-sterilized (with 0.45 μm-pore size filter) and was incubated at 37°C; positive control was incubated with 1% dimethyl sulfoxide (DMSO) at 37°C; blank was incubated at 4°C. All test-compounds dissolved in DMSO (final concentration of DMSO was less than 1%) were added in 5% BSA-0.5M G6P. After 10 day-incubation 5% BSA-0.5M G6P with a compound, positive control and blank were dialyzed against 2L phosphate buffered saline for 24 hours (fractional molecular weight: 12,000-14,000). The dialyzed solution was diluted in water 4 times and was determined the fluorescence (ex. 370 nm-em. 440 nm). The protein concentration of the dialyzed solution (10 μL of

which was diluted to 20 times with distilled water) was determined by Lowry-method and the fluorescence was expressed per mg protein. Control (100%) was positive control minus blank. Anti-glycation effect was calculated as the percentage of the control.

compound No.	concentration	% decrease
I-1a-1	100 μg/ml (0.24mM)	42.3
I-1a-2	100 μg/ml (0.38mM)	24.1
I-1a-3	100 μg/ml (0.32mM)	34.1
CS-045	100 μg/ml	10.1
CP-86325	100 μg/ml	10.3
aminoguanidine	(1 mM)	21.4
aminoguanidine	(10mM)	48.9
aminoguanidine	(100mM)	80.2



aminoguanidine

The compounds of the present invention exhibited anti-glycation activities stronger than aminoguanidine used as a control. CS-045 and CP-86325 did not exhibit anti-glycation activities.

TEST EXAMPLE 3: Measurement of aldose-reductase inhibitory activities

Rat kidney AR was prepared as follows; Rat kidney was perfused by ice-cold saline to remove blood and then homogenized in a Teflon homogenizer with 3 time volumes of cold 5 mM Tris-HCℓ buffer (pH 7.4). The homogenate

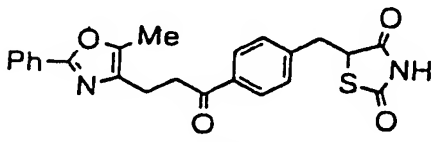
was centrifuged at 45,000 x g for 40 minutes to remove insoluble materials, and the supernatant fraction was used as an aldose reductase sample.

Determination of AR and effects of test compounds

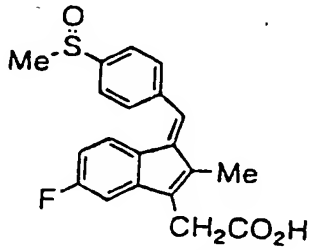
AR activity was assayed by the modified method of Inukai et al. (Jpn. J. Pharmacol. 61, 221-227, 1993). The absorbance of NADPH (340 nm), oxidation of the co-factor for AR, was determined by spectrophotometer (UV-240, Shimadzu, Kyoto). The assay was carried out in 0.1M sodium phosphate (pH 6.2) containing 0.4M lithium sulfate, 0.15 mM NADPH, the enzyme, various concentrations of test compounds and 10 mM DL-glyceraldehyde. The reference blank contained all of the above ingredients, except for DL-glyceraldehyde. The reaction was started by addition of the substrate (DL-glyceraldehyde). The reaction rate was measured at 30°C for 2 minutes. All test compounds were dissolved in dimethyl sulfoxide (DMSO). The final concentration of DMSO in reaction mixture never exceeded 1%. The effects of inhibitors were estimated as the concentration of test compounds required for 50% inhibition of enzyme activity (IC_{50}).

Aldose-reductase inhibitory activities

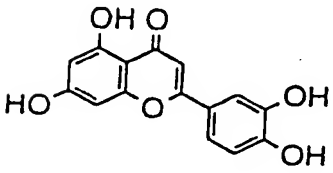
Compound No.	IC_{50}(M)
I-Ia-3	1.25×10^{-5}
I-Ia-6	1.40×10^{-5}
Sulindac	2.4×10^{-5}
Guercetin	$> 3 \times 10^{-5}$
Alrestatin	$>10 \times 10^{-5}$
CS-045	$>10 \times 10^{-5}$
CP-86325	$> 3 \times 10^{-5}$



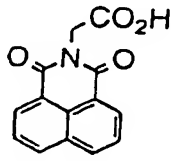
CP-86325



Sulindac



Quercetin



Alrestatin

The compounds of the present invention exhibited stronger aldose-reductase inhibitory activities than sulindac, quercetin or alrestatin used as control. Further, CS-045 and CP-86325 exhibited no activities.

FORMULATION EXAMPLE 1

Tablets

The compound of the present invention	1.0 g
Lactose	5.0 g
Crystal cellulose powder	8.0 g
Corn starch	3.0 g
Hydroxypropyl cellulose	1.0 g
CMC-Ca	1.5 g
Magnesium stearate	0.5 g
Total	20.0 g

The above components were mixed by a usual method and then tabletted to produce 100 tablets each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 2

Capsules

The compound of the present invention	1.0 g
Lactose	3.5 g
Crystal cellulose powder	10.0 g
Magnesium stearate	0.5 g
Total	15.0 g

The above components were mixed by a usual method and then packed in No. 4 gelatin capsules to obtain 100 capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 3

Soft capsules

The compound of the present invention	1.00 g
PEG (polyethylene glycol) 400	3.89 g
Saturated fatty acid triglyceride	15.00 g
Peppermint oil	0.01 g
Polysorbate 80	0.10 g
Total	20.00 g

The above compounds were mixed and packed in No. 3 soft gelatin capsules by a usual method to obtain 100 soft capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 4

Ointment

The compound of the present invention	1.0 g (10.0 g)
Liquid paraffin	10.0 g (10.0 g)
Cetanol	20.0 g (20.0 g)
White vaseline	68.4 g (59.4 g)
Ethylparaben	0.1 g (0.1 g)
l-menthol	0.5 g (0.5 g)
Total	100.0 g

The above components were mixed by a usual method to obtain a 1% (10%) ointment.

FORMULATION EXAMPLE 5

Suppository

The compound of the present invention	1.0 g
Witepsol H15*	46.9 g
Witepsol W35*	52.0 g
Polysorbate 80	0.1 g
Total	100.0 g

*: Trademark for triglyceride compound

The above components were melt-mixed by a usual method and poured into suppository containers, followed by cooling for solidification to obtain 100 suppositories of 1 g each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 6

Granules

The compound of the present invention	1.0 g
Lactose	6.0 g
Crystal cellulose powder	6.5 g
Corn starch	5.0 g
Hydroxypropyl cellulose	1.0 g
Magnesium stearate	0.5 g
Total	20.0 g

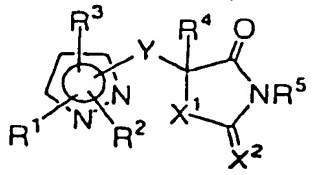
The above components were granulated by a usual method and packaged to obtain 100 packages each containing 200 mg of the granules so that each package contains 10 mg of the active ingredient.

INDUSTRIAL APPLICABILITY

Since the compound of the present invention has a hypoglycemic effect, an anti-glycation activity and an aldose-reductase inhibitory activity and has less toxicity, it is useful for preventing or treating diabetic complications including diabetic eye diseases (such as diabetic cataract and diabetic retinopathy), diabetic neuropathy, diabetic nephropathy, diabetic gangrene, and the like.

CLAIMS:

1. A pyrazole type thiazolidine compound of the following formula (I) and its salt:



(I)

wherein X^1 is S or O;

X^2 is S, O or NH;

Y is CR^6R^7 (R^6 is a hydrogen atom, a C_1-C_7 alkyl group or a C_3-C_7 cycloalkyl group, and R^7 is a hydrogen atom, a C_1-C_7 alkyl group or a C_3-C_7 cycloalkyl group, or forms a bond together with R^4);

R^1 is a C_1-C_{10} alkyl group, a C_2-C_{10} alkenyl group, a C_2-C_{10} alkynyl group, a C_1-C_{10} alkoxy group, a C_2-C_{10} alkenyloxy group, a C_1-C_{10} alkylthio group, a C_1-C_{10} monoalkylamino group or a di-C_1-C_{10} alkylamino group (each of said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyloxy, C_1-C_{10} alkylthio, C_1-C_{10} monoalkylamino and di-C_1-C_{10} alkylamino groups may be substituted with a hydroxyl group or a C_1-C_7 alkyl group), or

$-V_k-W_l-Z$ (Z is a C_3-C_{10} cycloalkyl group, a C_3-C_7 cycloalkenyl group, a C_6-C_{14} aromatic group, a C_4-C_{12} heterocyclic aromatic group (said heterocyclic aromatic group may contain at most 5 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and

a nitrogen atom as constituents for the heterocyclic ring), or a C_4-C_6 heterocycloaliphatic group (said heterocycloaliphatic group may contain at most 3 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom as constituents for the heterocyclic ring) (each of said C_3-C_{10} cycloalkyl, C_3-C_7 cycloalkenyl, C_6-C_{14} aromatic, C_4-C_{12} heterocyclic aromatic and C_4-C_6 heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting of a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a

1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group),

W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, and

each of k and ℓ is 0 or 1),

-V-W-V-W-Z (V, W and Z are as defined above, and two V's and W's may, respectively, be the same or different),

-W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different),

-V-W-V-Z (V, W and Z are as defined above, and two V's may be the same or different), or

-W-V-Z (V, W and Z are as defined above);

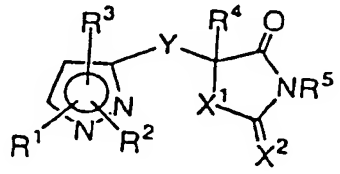
each of R^2 and R^3 is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group (said C_1-C_7 alkyl and C_3-C_7 cycloalkyl groups may be substituted with a hydroxyl group), a phenyl group, a naphthyl group, a benzyl group, a pyridyl group, a pyrimidinyl group, a pyridazinyl group, a furanyl group, a thienyl group, a pyrrolyl group, a pyrazolyl group, an imidazolyl group, a pyranyl group, a quinolyl group, a benzoxazolyl group, a benzothiazolyl group or a benzimidazolyl group (each of said phenyl, naphthyl, benzyl, pyridyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,

imidazolyl, pyranyl, quinolyl, benzoxazolyl, benzothiazolyl and benzimidazolyl groups may be substituted with at most 5 members selected from the group consisting of a hydroxyl group, a C_1-C_7 alkyl group, a C_1-C_7 alkoxy group and a halogen atom), and R^2 or R^3 may further be a halogen atom when it is bonded to a carbon atom at the 3-, 4- or 5-position of the pyrazole ring;

R^4 is a hydrogen atom or a C_1-C_7 alkyl group, or forms a bond together with R^7; and

R^5 is a hydrogen atom or a carboxymethyl group.

2. The pyrazole type thiazolidine compound and its salt according to Claim 1, wherein the compound of the formula (I) is represented by the following formula (Ia):



(Ia)

wherein R^1 is a C_1-C_{10} alkyl group, a C_2-C_{10} alkenyl group, a C_2-C_{10} alkynyl group, a C_1-C_{10} alkoxy group, a C_2-C_{10} alkenyloxy group, a C_1-C_{10} alkylthio group, a C_1-C_{10} monoalkylamino group or a di-C_1-C_{10} alkylamino group (each of said C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyloxy, C_1-C_{10} alkylthio, C_1-C_{10} monoalkylamino and di-C_1-C_{10} alkylamino groups may be substituted with a hydroxyl group or a C_1-C_7 alkyl group), or

$-V_k-W_l-Z$ (among groups of Z as defined for the formula (I), said C_3-C_{10} cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, or adamantyl, said C_3-C_7 cycloalkenyl group is cyclohexenyl, cyclopentadienyl, 2-bicylo[2.2.1]heptenyl or 2,5-bicyclo[2.2.1]heptadienyl, said C_6-C_{14} aromatic group is phenyl, naphthyl, indenyl, indanyl or fluorenyl, said C_4-C_{12} heterocyclic aromatic group is furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, furazanyl, pyrazolyl, oxopyrazolyl, imidazolyl, oxoimidazolyl, triazolyl, triazolonyl, tetrazolyl, pyranyl, pyridyl, pyridonyl, pyridazinyl, pyridazinonyl, pyrimidinyl, pyrimidinonyl, pyrazinyl, triazinyl, tetrazinyl, indolyl, quinolyl, quinolonyl, benzofuranyl, benzothienyl, isoquinolyl, isoquinolonyl, benzoxazolyl, benzothiazolyl, benzopyrazolyl, benzimidazolyl, benzotriazolyl, benzopyranyl, indolizinyl, purinyl, phthalazinyl, oxophthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzodioxanyl, oxonaphthalenyl, dihydrobenzofuranyl, benzothiazinyl, pteridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[5,1-c][1,2,4]triazinyl, thiazolo[3,2-b]triazolyl, benzopyrano[2,3-b]pyridyl, 5H-benzopyrano[2,3-b]pyridonyl, xanthenyl, phenoxathiinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, or

thianthrenyl, and said C_4-C_6 heterocycloaliphatic group is piperidyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, morpholinyl, or tetrahydrofuranyl, (each of said C_3-C_{10} cycloalkyl, C_3-C_7 cycloalkenyl, C_6-C_{14} aromatic, C_4-C_{12} heterocyclic aromatic and C_4-C_6 heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting of a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group and a thiazolidindion-5-yl

methyl group),

V is O, S, SO, SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group),

W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, and

each of k and ℓ is 0 or 1),

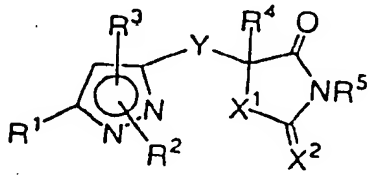
-V-W-V-W-Z (V, W and Z are as defined above, and two V's and W's may, respectively, be the same or different),

-W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different),

-V-W-V-Z (V, W and Z are as defined above, and two V's may be the same or different), or

-W-V-Z (V, W and Z are as defined above).

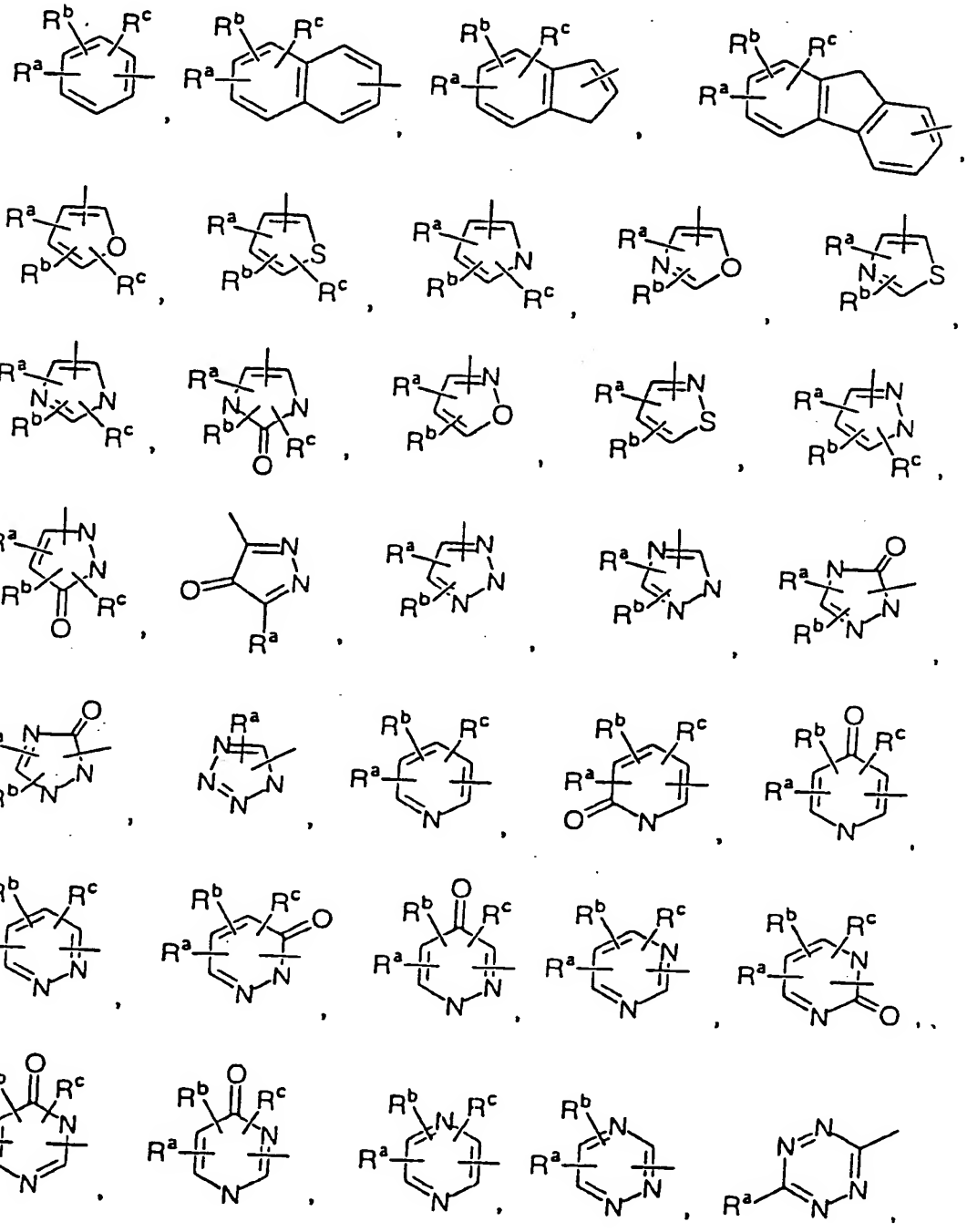
3. The pyrazole type thiazolidine compound and its salt according to Claim 2, wherein the compound of the formula (Ia) is represented by the formula (Ib):

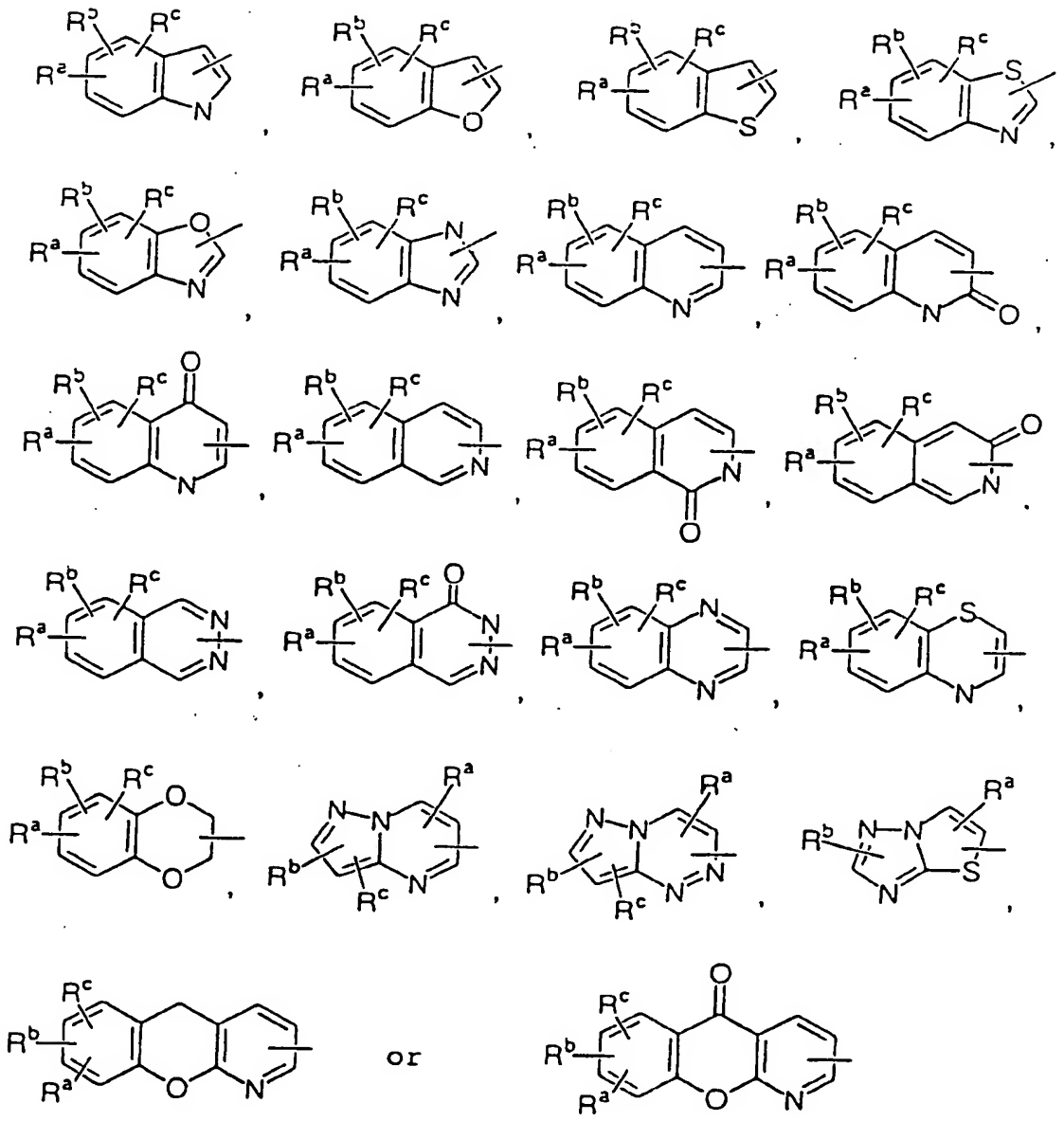


(Ib)

4. The pyrazole type thiazolidine compound and its salt according to Claim 3, wherein R^1 is -V-W-Z, -W-Z, -V-W-V-W-Z, -W-V-W-Z, -V-W-V-Z or -W-V-Z (V is O, S or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3

of hydroxyl, oxo and C_1-C_7 alkyl groups, when two V's or W's are present, such V's or W's may be the same or different, and Z is





or

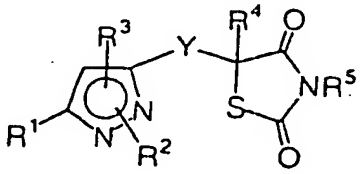
wherein each of R^a and R^b is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a C_1-C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a C_1-C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group or a hydroxymethyl group);

R^2 or R^3 is a hydrogen atom, a C_1-C_4 alkyl group, a C_3-C_6 cycloalkyl group, a phenyl group, a naphthyl group,

a benzyl group or a pyridyl group, when it is on the nitrogen atom at the 1-position of the pyrazole ring; and

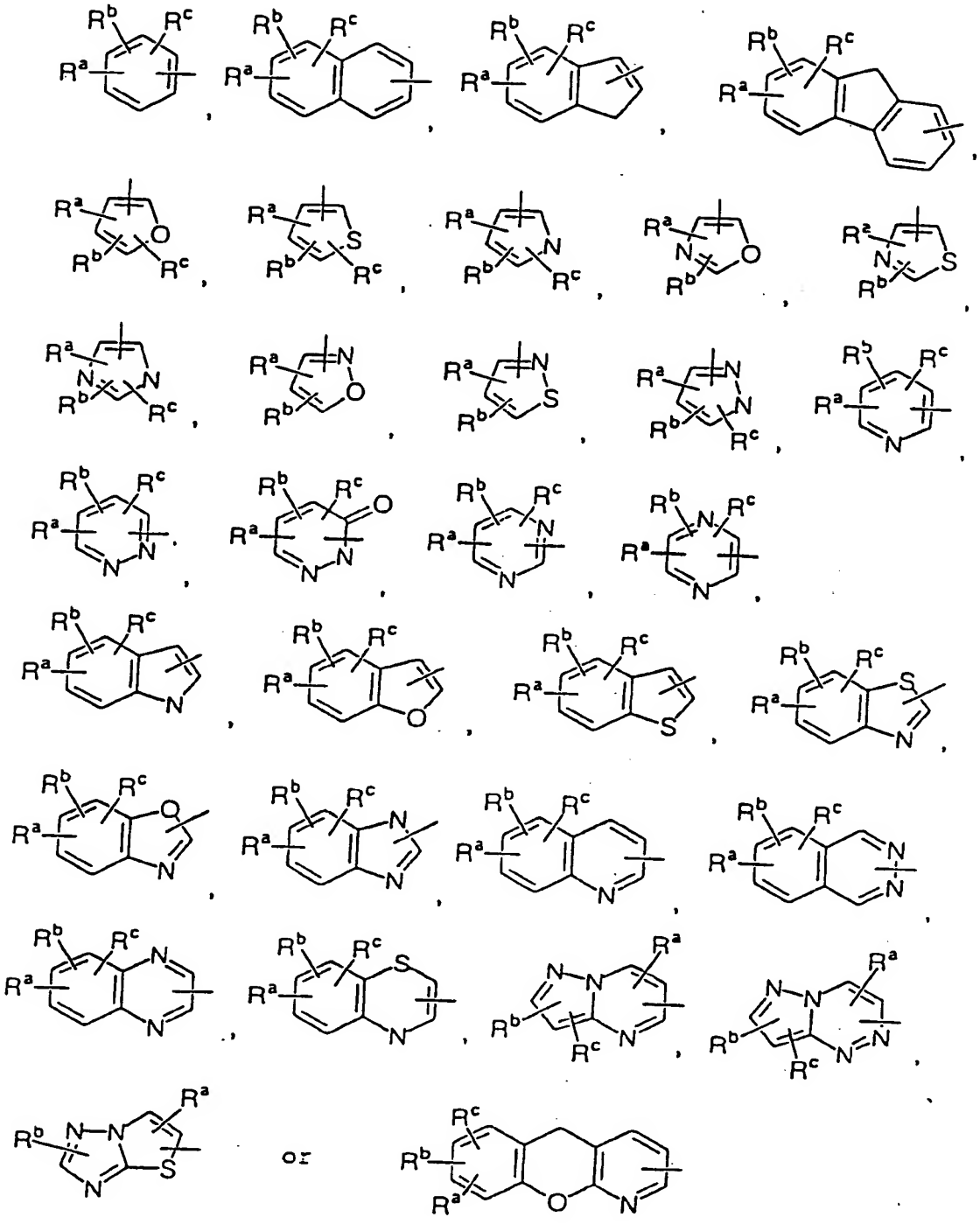
R^2 or R^3 is a hydrogen atom, a C_1-C_4 alkyl group, a phenyl group or a halogen atom, when it is on the carbon atom at the 4-position of the pyrazole ring.

5. The pyrazole type thiazolidine compound and its salt according to Claim 4, wherein said compound is represented by the formula:



wherein Y is CR^6R^7 (R^6 is a hydrogen atom or a methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4);

R^1 is -V-W-Z, -W-Z, -V-W-V-W-Z, -W-V-W-Z, -V-W-V-Z or -W-V-Z (V is O, S or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1-C_7 alkyl groups, when two V's or W's are present, such V's or W's may be the same or different, and Z is



wherein each R^a and R^b is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_3-C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1-C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a phenoxy group, a benzyloxy group, a phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α-naphthyl, β-naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group, a C_1-C_3 alkoxy group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1-C_7 alkyl group, a C_3-C_7 cycloalkyl group or a hydroxymethyl group);

R^4 is a hydrogen atom or a methyl group, or forms a bond together with R^7;

R^5 is a hydrogen atom or a carboxymethyl group.

6. The pyrazole type thiazolidine compound and its salt

according to Claim 5, wherein:

R^1 is -O-W-Z, wherein W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 2 of hydroxyl, oxo and C_1-C_7 alkyl groups (provided that the first carbon atom bonded with the oxygen atom is not substituted with a hydroxyl group or an oxo group).

7. The pyrazole type thiazolidine compound and its salt according to Claim 5, wherein:

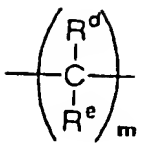
R^1 is -O-W-V-W-Z, -W-V-W-Z, -O-W-V-Z or -W-V-Z, wherein V is O or NR^8 (R^8 is a hydrogen atom or a C_1-C_3 alkyl group), W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 2 of hydroxyl, oxo and C_1-C_7 alkyl groups (provided that the first carbon atom bonded with the oxygen atom is not substituted with a hydroxyl group or an oxo group when two W's are present, such W's may be the same or different).

8. The pyrazole type thiazolidine compound and its salt according to Claim 5, wherein:

R^1 is -W-Z, wherein W is a divalent C_1-C_6 saturated or C_2-C_6 unsaturated hydrocarbon group which may be substituted with at most 2 hydroxyl, oxo and C_1-C_7 alkyl groups.

9. The pyrazole type thiazolidine compound and its salt according to Claim 6, wherein:

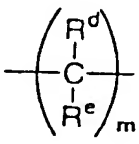
R^1 is -O-W-Z, wherein W is



wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond (provided that R^d and R^e on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group).

10. The pyrazole type thiazolidine compound and its salt according to Claim 7, wherein:

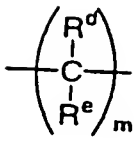
R^1 is -O-W-V-W-Z, -W-V-W-Z, -O-W-V-Z or -W-V-Z, wherein W is



wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond (provided that R^d and R^e on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group).

11. The pyrazole type thiazolidine compound and its salt according to Claim 8, wherein:

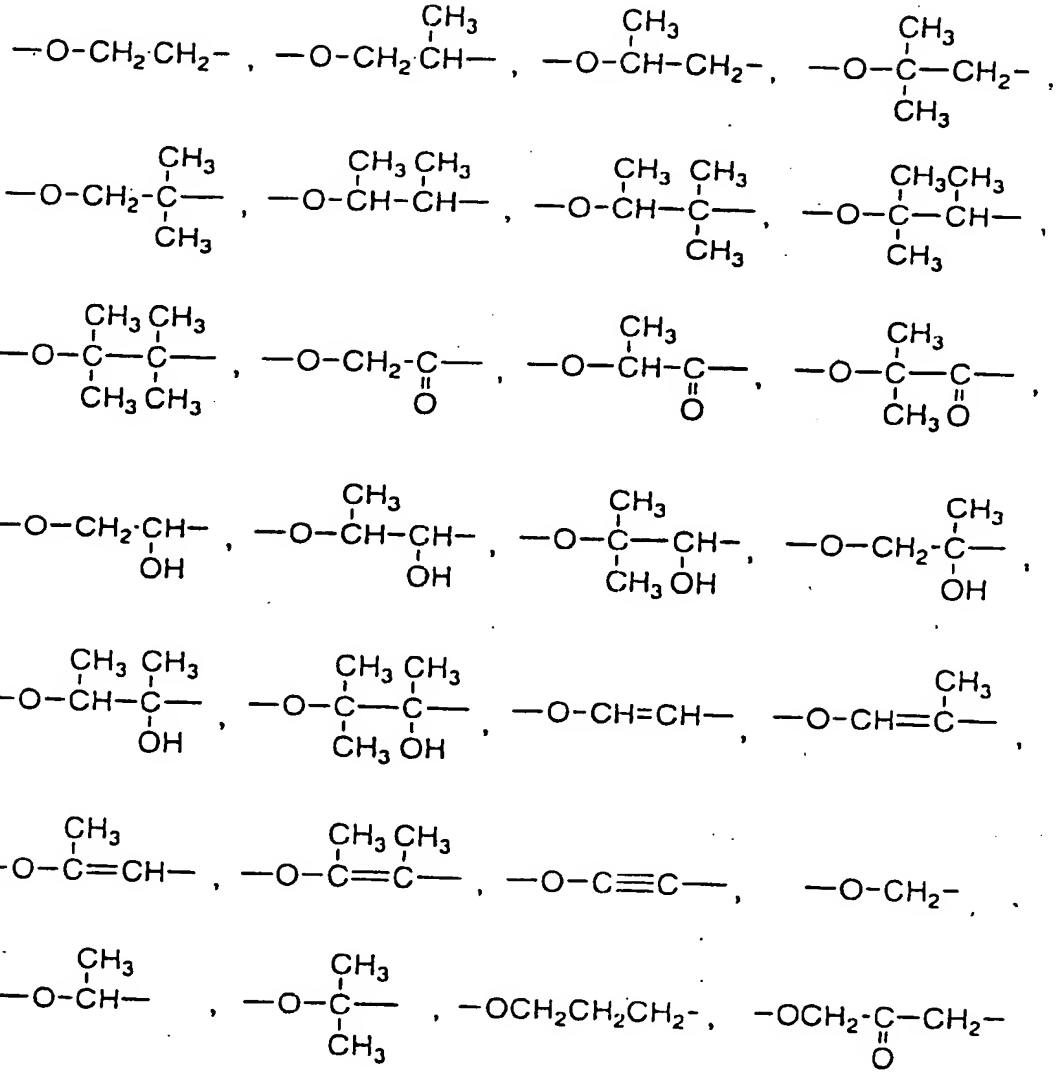
R^1 is -W-Z, wherein W is

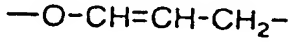


wherein m is from 1 to 5, each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond.

12. The pyrazole type thiazolidine compound and its salt according to Claim 9, wherein:

R^1 is -O-W-Z, wherein -O-W is

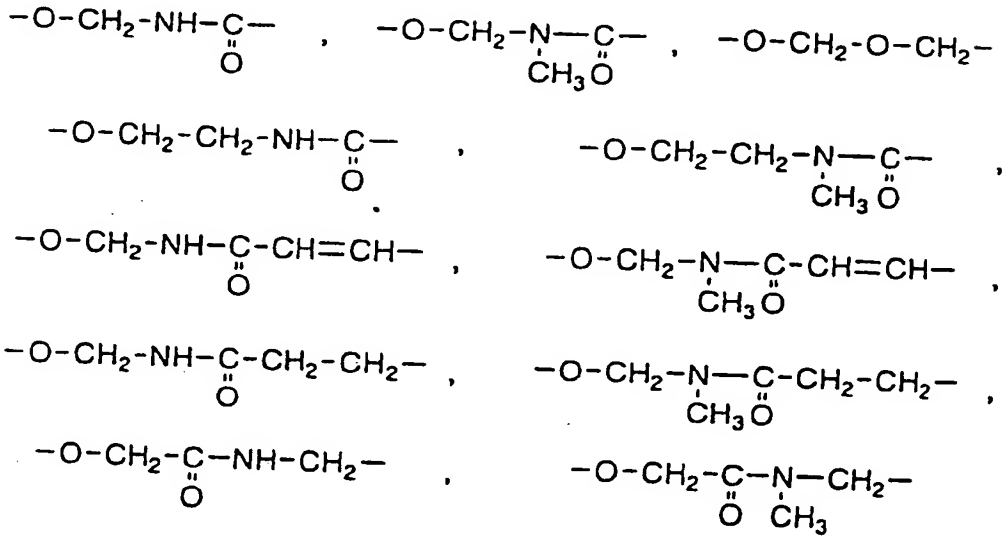


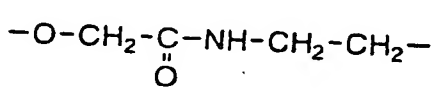
or 

13. The pyrazole type thiazolidine compound and its salt according to Claim 10, wherein:

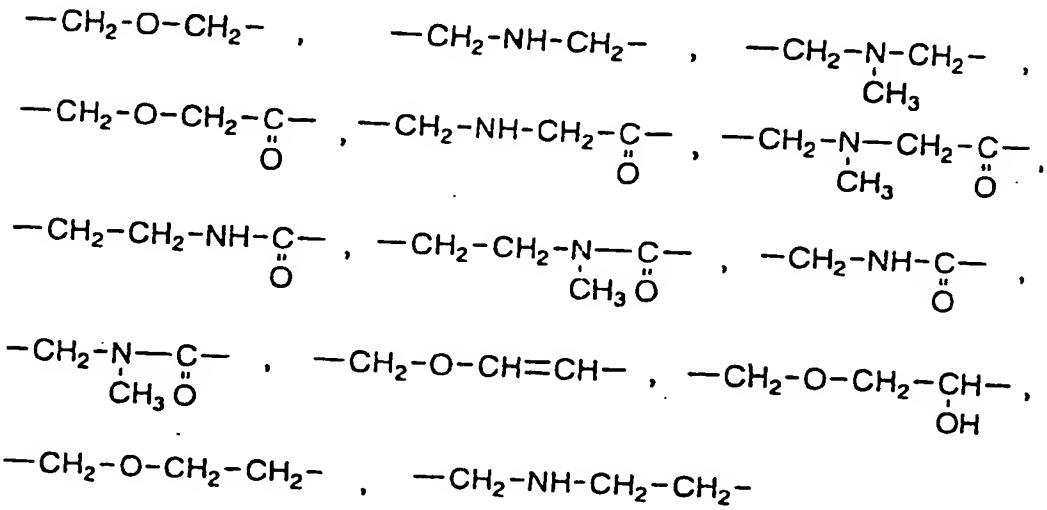
R^1 is -O-W-V-W-Z, -W-V-W-Z, -O-W-V-Z or -W-V-Z,

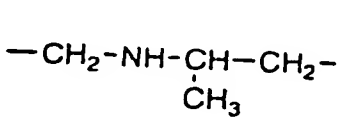
wherein -O-W-V-W- is



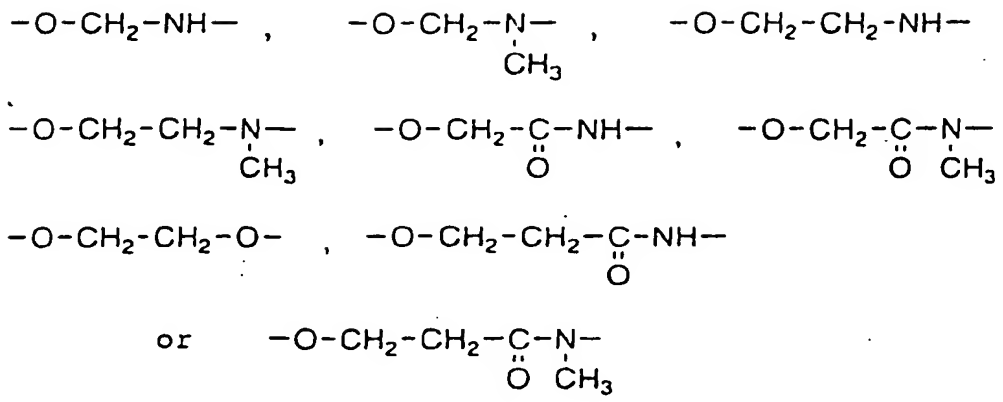
or 

-W-V-W- is

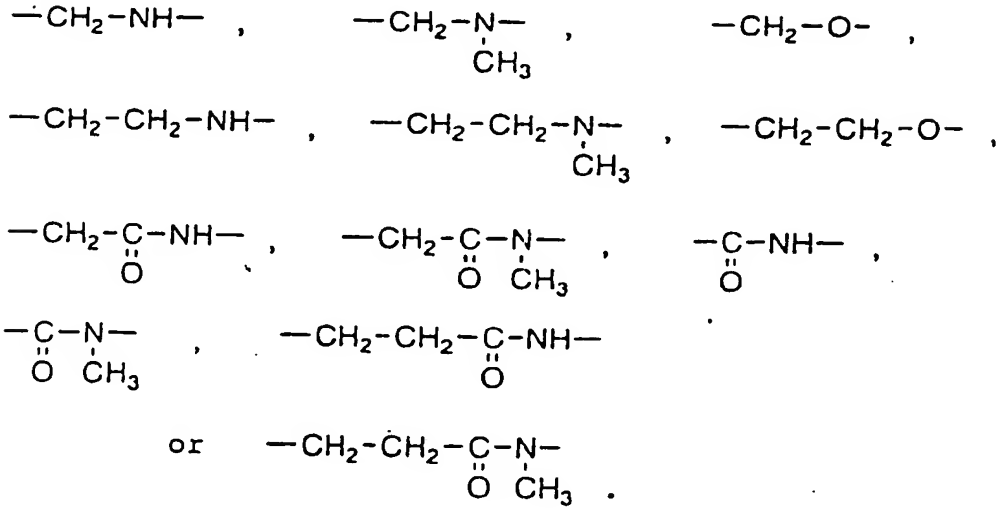


or 

-O-W-V- is

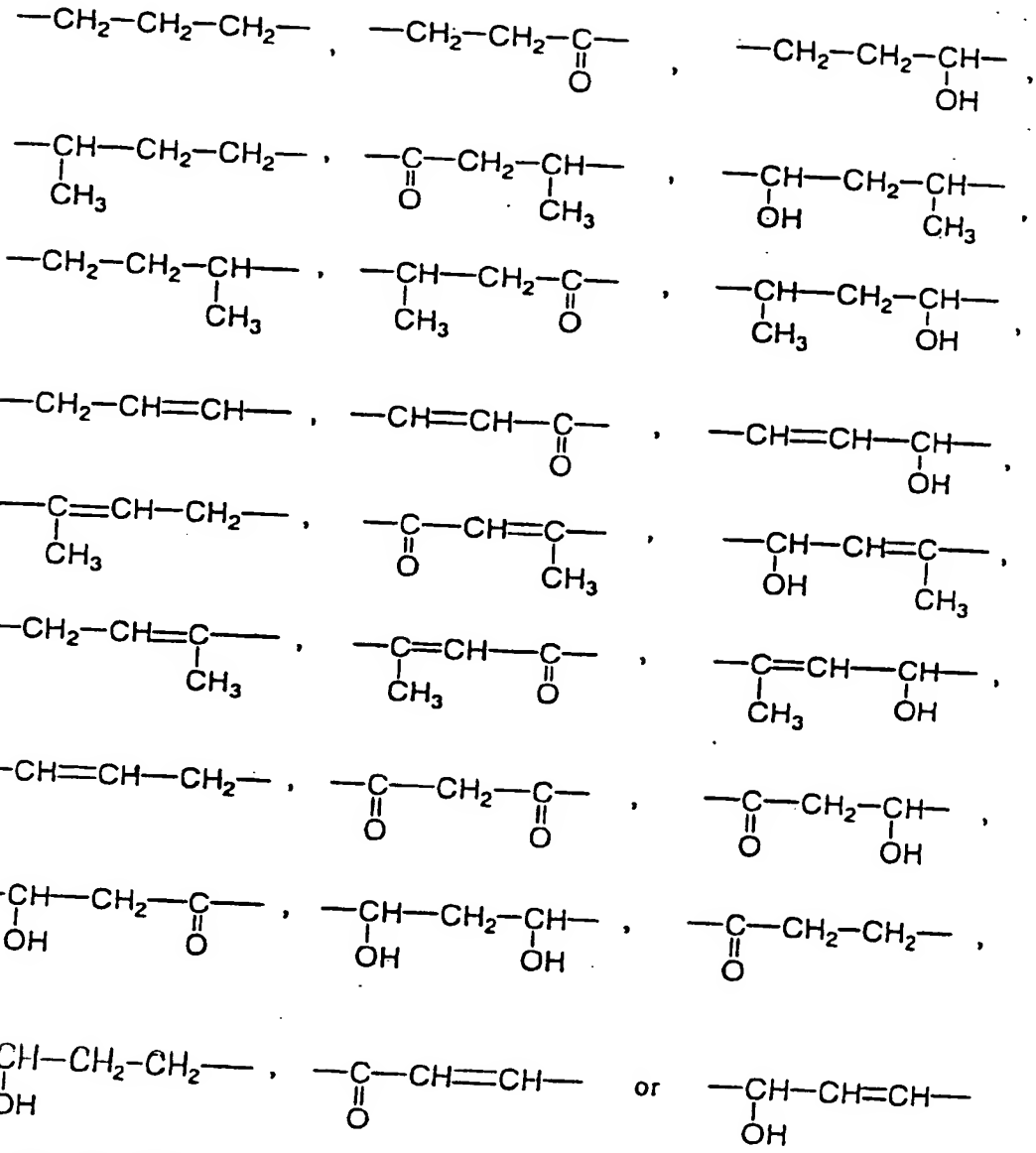


and -W-V- is



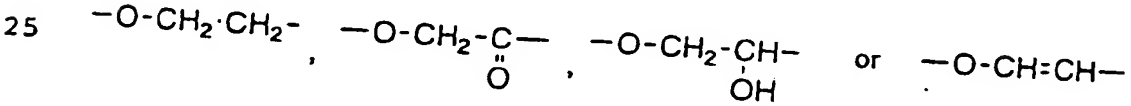
14. The pyrazole type thiazolidine compound and its salt according to Claim 11, wherein:

R^1 is -W-Z, wherein W is



15. The pyrazole type thiazolidine compound and its salt according to Claim 12, wherein:

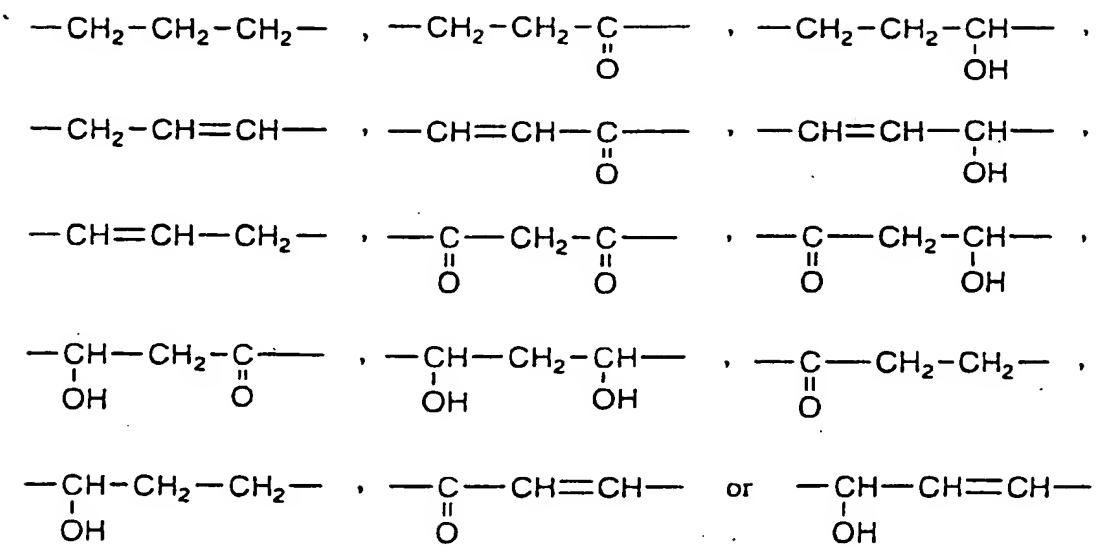
R^1 is -O-W-Z, wherein -O-W- is



16. The pyrazole type thiazolidine compound and its salt

according to Claim 14, wherein:

R^1 is -W-Z, wherein W is



17. The pyrazole type thiazolidine compound and its salt according to Claim 6, 7 or 8, wherein:

Y is $-CH_2-$; and

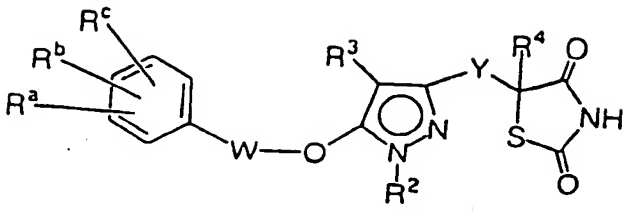
R^4 is a hydrogen atom.

18. The pyrazole type thiazolidine compound and its salt according to Claim 6, 7 or 8, wherein:

Y is CHR^7 (R^7 forms a bond together with R^4); and

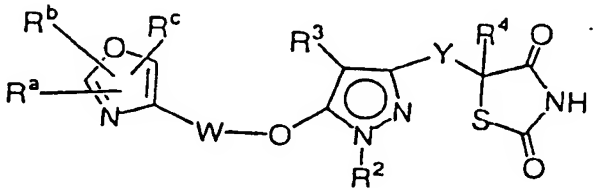
R^4 forms a bond together with R^7.

19. The pyrazole type thiazolidine compound and its salt according to Claim 15, which is represented by the formula:



wherein each of R^a, R^b and R^c is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom or a phenyl group (said phenyl group may be substituted with at most 3 of a methyl group, a methoxy group and a chlorine atom), R^2 is a hydrogen atom, a C_1-C_7 alkyl group or a phenyl group, R^3 is a hydrogen atom or a C_1-C_7 alkyl group, Y is CR^6R^7 (R^6 is a hydrogen atom or a methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4), and R^4 is a hydrogen atom, or forms a bond together with R^7.

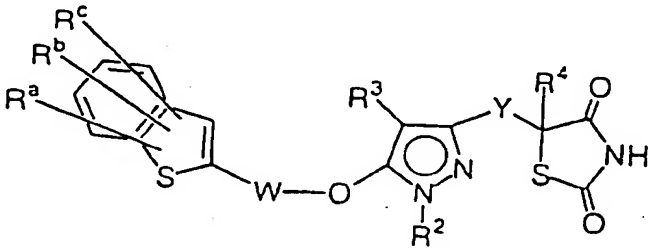
20. The pyrazole type thiazolidine compound and its salt according to Claim 15, which is represented by the formula:



wherein each of R^a, R^b and R^c is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom or a phenyl group (said phenyl group may be substituted with at most 3 of a methyl group, a methoxy group and a

chlorine atom), R^2 is a hydrogen atom, a C_1-C_7 alkyl group or a phenyl group, R^3 is a hydrogen atom or a C_1-C_7 alkyl group, Y is CR^6R^7 (R^6 is a hydrogen atom or a methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4), and R^4 is a hydrogen atom, or forms a bond together with R^7.

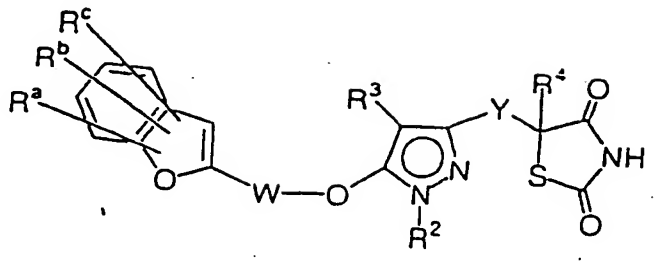
21. The pyrazole type thiazolidine compound and its salt according to Claim 15, which is represented by the formula:



wherein each of R^a, R^b and R^c is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom or a phenyl group (said phenyl group may be substituted with at most 3 of a methyl group, a methoxy group and a chlorine atom), R^2 is a hydrogen atom, a C_1-C_7 alkyl group or a phenyl group, R^3 is a hydrogen atom or a C_1-C_7 alkyl group, Y is CR^6R^7 (R^6 is a hydrogen atom or a methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4), and R^4 is a hydrogen atom, or forms a bond together with R^7.

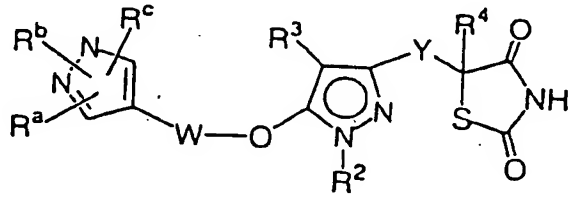
22. The pyrazole type thiazolidine compound and its salt according to Claim 15, which is represented by the

formula:



wherein each of R^a, R^b and R^c is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom or a phenyl group (said phenyl group may be substituted with at most 3 of a methyl group, a methoxy group and a chlorine atom), R^2 is a hydrogen atom, a C_1-C_7 alkyl group or a phenyl group, R^3 is a hydrogen atom or a C_1-C_7 alkyl group, Y is CR^6R^7 (R^6 is a hydrogen atom or a methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4), and R^4 is a hydrogen atom, or forms a bond together with R^7.

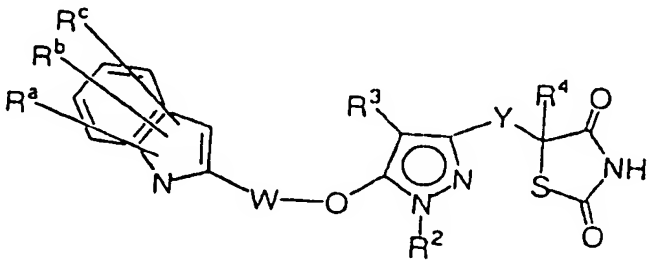
23. The pyrazole type thiazolidine compound and its salt according to Claim 15, which is represented by the formula:



wherein each of R^a, R^b and R^c is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom or a

phenyl group (said phenyl group may be substituted with at most 3 of a methyl group, a methoxy group and a chlorine atom), R^2 is a hydrogen atom, a C_1-C_7 alkyl group or a phenyl group, R^3 is a hydrogen atom or a C_1-C_7 alkyl group, Y is CR^6R^7 (R^6 is a hydrogen atom or a methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4), and R^4 is a hydrogen atom, or forms a bond together with R^7.

24. The pyrazole type thiazolidine compound and its salt according to Claim 15, which is represented by the formula:



wherein each of R^a, R^b and R^c is independently a hydrogen atom, a C_1-C_7 alkyl group, a C_1-C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom or a phenyl group (said phenyl group may be substituted with at most 3 of a methyl group, a methoxy group and a chlorine atom), R^2 is a hydrogen atom, a C_1-C_7 alkyl group or a phenyl group, R^3 is a hydrogen atom or a C_1-C_7 alkyl group, Y is CR^6R^7 (R^6 is a hydrogen atom or a methyl group, and R^7 is a hydrogen atom, or forms a bond together with R^4), and R^4 is a hydrogen atom, or forms a bond together with R^7.

25. A hypoglycemic agent containing the pyrazole type thiazolidine compound or its salt according to Claim 1 as an active agent.

26. An anti-glycation agent containing the pyrazole type thiazolidine compound or its salt according to Claim 1 as an active agent.

27. An aldose reductase inhibitor containing the pyrazole type thiazolidine compound or its salt according to Claim 1 as an active agent.

28. A pharmaceutical agent for preventing and treating diabetes mellitus and diabetic complications, which contains the pyrazole type thiazolidine compound or its salt according to Claim 1 as an active agent.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/JP 95/02041

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-389699	03-10-90	WO-A-	8908652	21-09-89
		CA-A-	1328265	05-04-94
		CN-B-	1026234	19-10-94
		FI-B-	92696	15-09-94
		NO-B-	178068	09-10-95
		PT-B-	89922	01-03-95
		US-A-	5330998	19-07-94
EP-A-332331	13-09-89	WO-A-	8908650	21-09-89
		CA-A-	1328872	26-04-94
		DE-D-	68912952	24-03-94
		DE-T-	68912952	11-05-94
		PT-B-	89913	31-05-94
		US-A-	5061717	29-10-91
		US-A-	5120754	09-06-92
		US-A-	5223522	29-06-93
EP-A-177353	09-04-86	WO-A-	8602073	10-04-86
		WO-A-	8606069	23-10-86
		AU-B-	583537	04-05-89
		AU-B-	4817685	10-04-86
		CA-A-	1263655	05-12-89
		JP-C-	1859452	27-07-94
		JP-A-	61085372	30-04-86
		US-A-	4725610	16-02-88
		SU-A-	1436876	07-11-88

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/JP 95/02041

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D417/14 C07D417/06 C07D413/14 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JUSTUS LIEBIGS ANN. CHEM., vol. 585, - 1954 pages 115-123, HUETTEL ET AL. see page 123, line 10 ---	1
A	EP-A-0 389 699 (PFIZER) 3 October 1990 see page 1; claim 1 ---	1-28
A	EP-A-0 332 331 (PFIZER) 13 September 1989 cited in the application see page 1; claim 1 ---	1-28
A	EP-A-0 177 353 (TAKEDA) 9 April 1986 cited in the application see page 1; claim 1 -----	1-28

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 January 1996	14.02.1996

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Lauro, P

Form PCT/ISA/210 (second sheet) (July 1992)